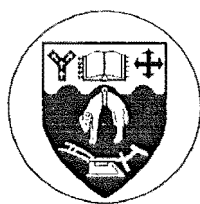


IPSO ATTACK OF
AROMATIC SYSTEMS

A thesis
presented for the degree
of
Doctor of Philosophy in Chemistry
in the
University of Canterbury
by
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University of Canterbury
Christchurch
New Zealand
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"Hallo!" said Piglet, "what are you doing?"

"Hunting," said Pooh.

"Hunting what?"

"Tracking something," said Winnie-the-Pooh very mysteriously.

"Tracking what?" said Piglet coming closer.

"That's just what I ask myself, What?"

"What do you think you'll answer?"

"I shall have to wait until I catch up with it," said Winnie-the-Pooh.

Winnie-the-Pooh

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ABSTRACT

This thesis concerns the chlorination reactions of a series of methyl and chloro substituted 4-chloro-6-methylphenols. The regioselectivity and mode of the chlorine addition reaction to the phenolic ring is examined with respect to the position of the substituents on the phenolic ring, and their properties of either donating or withdrawing electrons. It is shown that suppression of nucleophilic mechanisms of chlorine addition, which used to be achieved through the use of sodium acetate, can be accomplished more efficiently by the choice of acetic anhydride as a solvent.

Chlorine reacts with electron rich 2,6-dimethyl phenols by electrophilic mechanisms, with 2,3-addition appearing to be the favoured mode of reaction. This is illustrated by the reactions of two substituted phenols in Chapter Two.

Chapter Three describes the reactions of a dichloro methyl phenol which reacts with chlorine preferably by nucleophilic pathways. Electrophilic addition can be forced by the use of acetic anhydride, or by the addition of sodium acetate to the solvent, and the greater effectiveness of the former at suppressing nucleophilic addition is illustrated in this section. The stereochemistry of the chlorine addition is examined through the chlorination reactions of 2,4-dibromo-6-methylphenol.

In Chapter Four, it is shown that nucleophilic attack of chloride ion is the preferred reaction mode of electron deficient trichloro methyl phenols. The two phenols discussed in this Chapter also illustrate the necessity of a vacant C3 ring position for nucleophilic addition to occur. Blocking this site with a chloro substituent slows the reaction drastically.

The behaviour of chlorine towards two dichloro dimethyl phenols is examined in Chapter Five. Again, the necessity of an unsubstituted C3 site for nucleophilic addition is demonstrated, with the switching of mechanism from nucleophilic with C3 vacant, to electrophilic with a methyl substituted C3 position.

Finally, use of Semi-Empirical calculations is made throughout this thesis, to estimate the relative stabilities of intermediate species and for a theoretical study of the interconversion of various cyclohexadienones by [1,5]-sigmatropic shifts of chlorine.

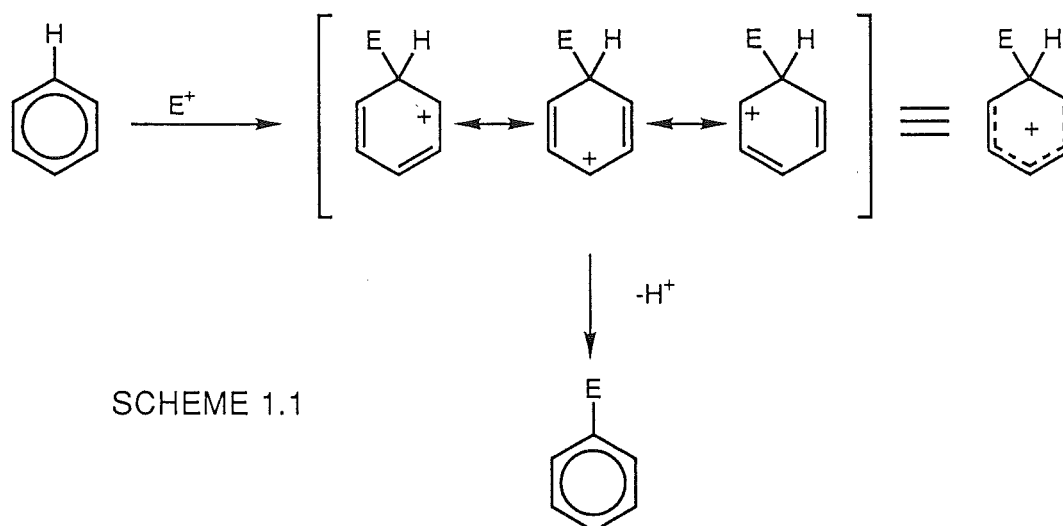
CHAPTER ONE

INTRODUCTION

1.1 Electrophilic Aromatic Substitution:

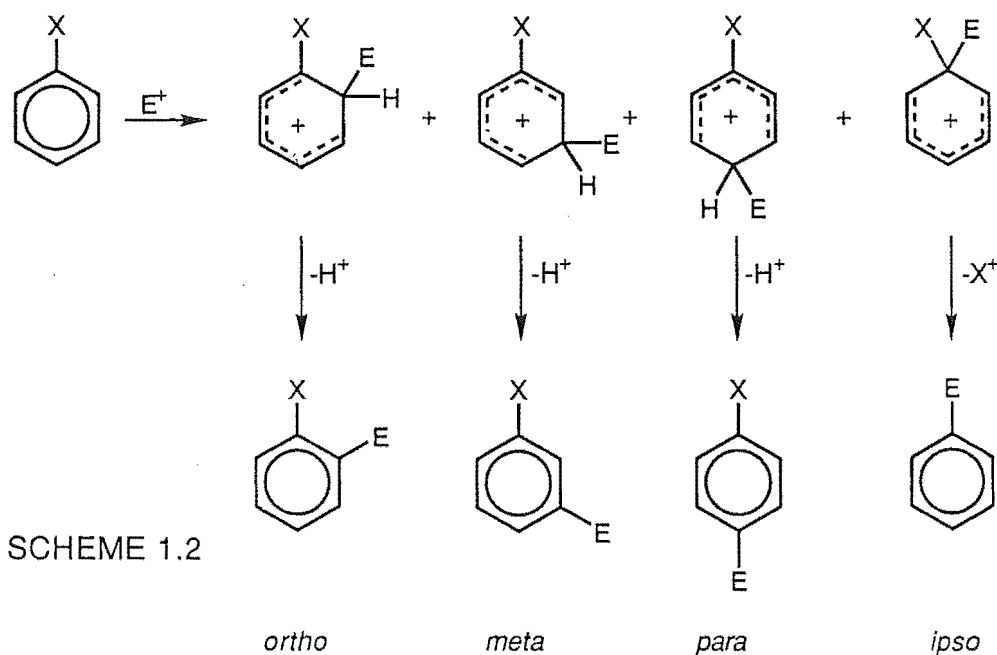
Electron rich aromatic rings are attractive targets for electrophiles, species bearing a formal positive charge or possessing a dipole, and as substitution retains the inherent stability of aromaticity, this process is favoured over addition. A number of reviews cover the general aspects of these types of reaction.¹⁻⁴

Electrophilic substitution of an aromatic compound occurs via a Wheland intermediate⁵, a resonance stabilised cation, the canonical forms of which may be represented in the following way (Scheme 1.1).

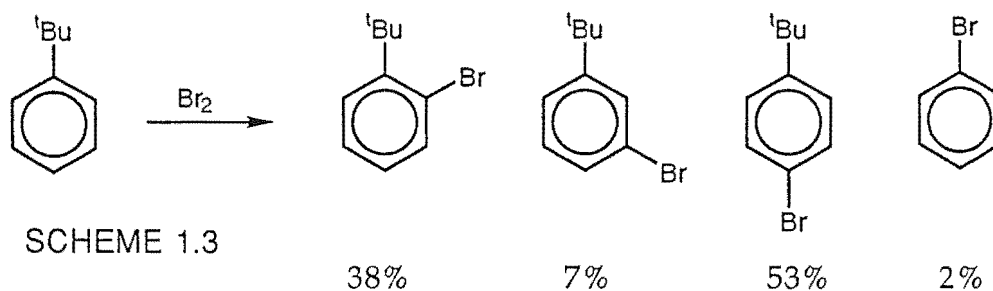


For a monosubstituted aromatic compound attack of the electrophile may occur at either the *ortho*, *meta* or *para* positions giving the appropriate Wheland intermediate, followed by loss of a proton to regenerate the aromatic character. Another option for substitution exists in the attack of the electrophile at the carbon bearing the substituent, requiring loss of the substituent to re-establish the aromaticity. Perrin and Skinner called this

mode of substitution *ipso* in 1971.⁶



An example demonstrating this type of substitution is shown in the bromination of *tert*-butylbenzene, where the following product ratios were found (Scheme 1.3).⁷



The bromobenzene almost certainly arises from electrophilic attack by bromine on the carbon bearing the *tert*-butyl group, followed by loss of the comparatively stable *tert*-butyl cation.

1.2 Ipso Attack:

Several possibilities exist for neutralising the positive charge of the Wheland intermediate. Often the driving force behind these processes is

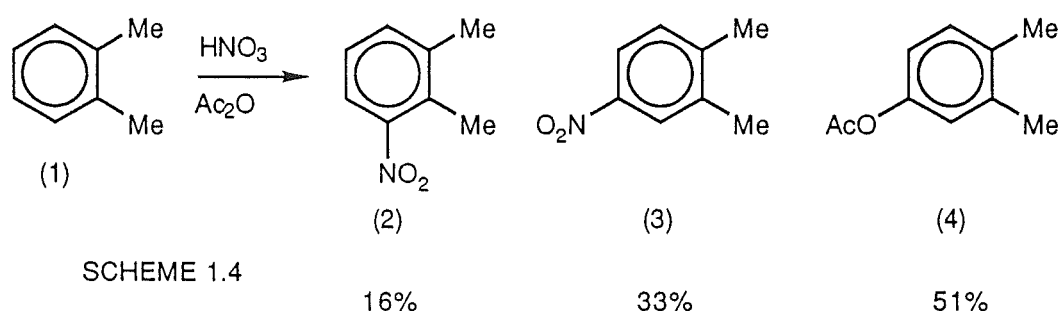
the stability gained in rearomatisation of the ring. Loss of either the electrophile or *ipso* substituent, nucleophilic capture, modification of another substituent and substituent migration have all been observed and documented in the literature. These will be examined in more detail.

1.2.1 Substitution

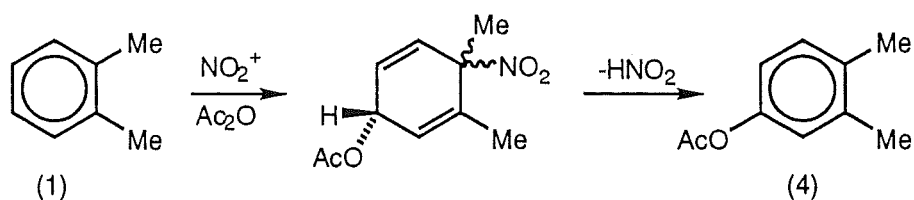
As shown above in the bromination of *tert*-butylbenzene loss of the *ipso* substituent as the *t*-butyl cation will regenerate the aromaticity. This process occurs only if the cation is stable.

1.2.2 Capture of a Nucleophile

Due to their cationic nature Wheland intermediates are susceptible to nucleophilic capture if suitable species exist in the reaction medium. One example occurs in the nitration of *o*-xylene (1) in acetic anhydride (Scheme 1.4). Formation of the major product of the reaction, 4-acetoxy-*o*-xylene (4), was attributed to attack of the Wheland intermediate by the nucleophilic solvent.⁸

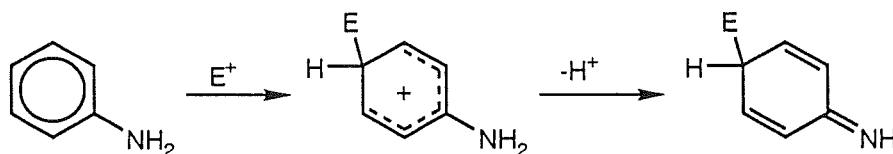


This was later confirmed by the isolation of two epimeric intermediates, which upon loss of nitrous acid gave the observed product (Scheme 1.5).⁹



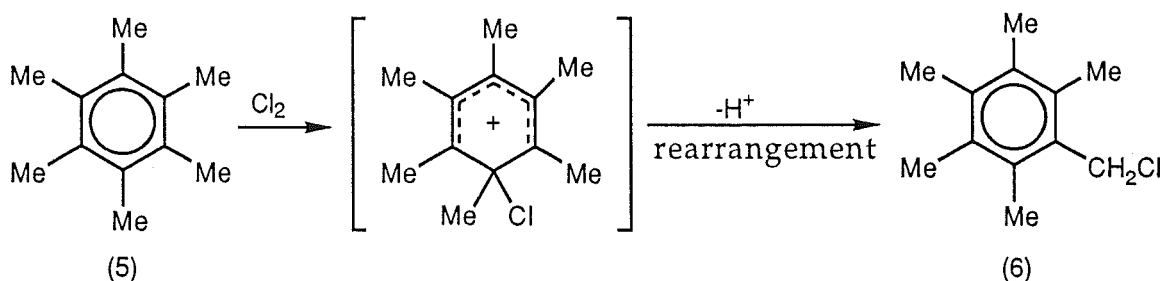
1.2.3 Side Chain Modification

Neutralisation of the positive charge through alterations in ring substituents is common, even though in some cases the aromatic stabilisation is lost. For example a Wheland intermediate arising from electrophilic attack on aniline may lose an amine proton to give rise to an imine structure (Scheme 1.6). Although the aromatic character is lost, loss of the proton from nitrogen will occur faster than loss of a proton from carbon. This is also true for phenolic systems, where proton loss from the oxygen is favoured resulting in the generation of a dienone moiety.



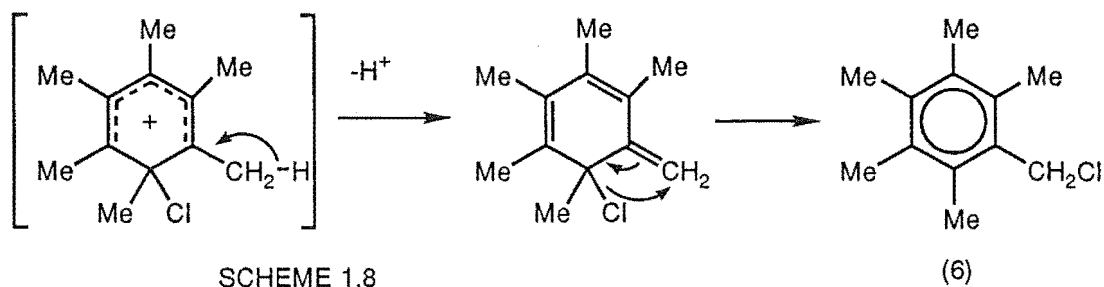
SCHEME 1.6

An example where the aromaticity is retained occurs in the chlorination of hexamethylbenzene (5) (Scheme 1.7).¹⁰ The major product from this reaction is a chloromethyl species (6). This reaction is second order in both chlorine and substrate and the rate is unaffected by light. This indicates the reaction does not involve free radical species, rather it occurs with an initial heterolytic electrophilic attack of the ring.



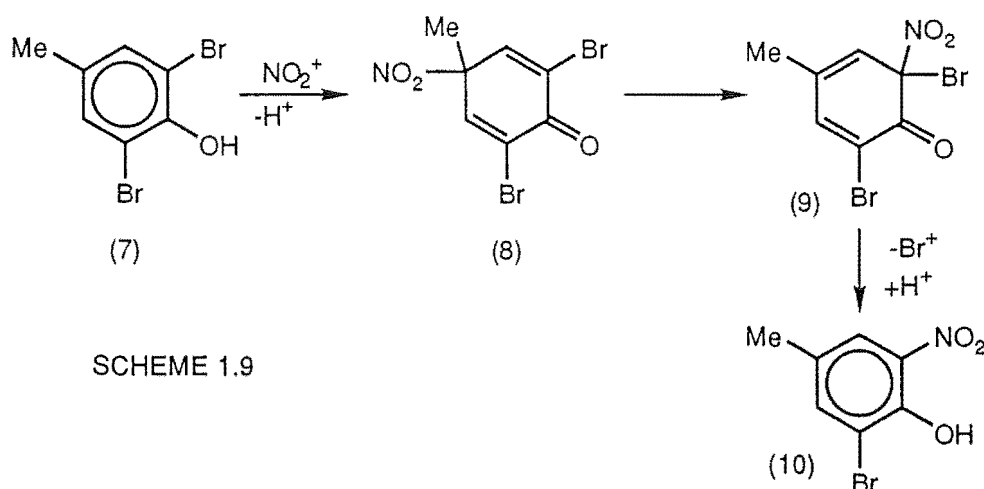
SCHEME 1.7

Several mechanisms were postulated for the rearrangement step, the most likely involving formation of a methylene derivative and intramolecular transfer of the chlorine atom (Scheme 1.8, over).¹⁰



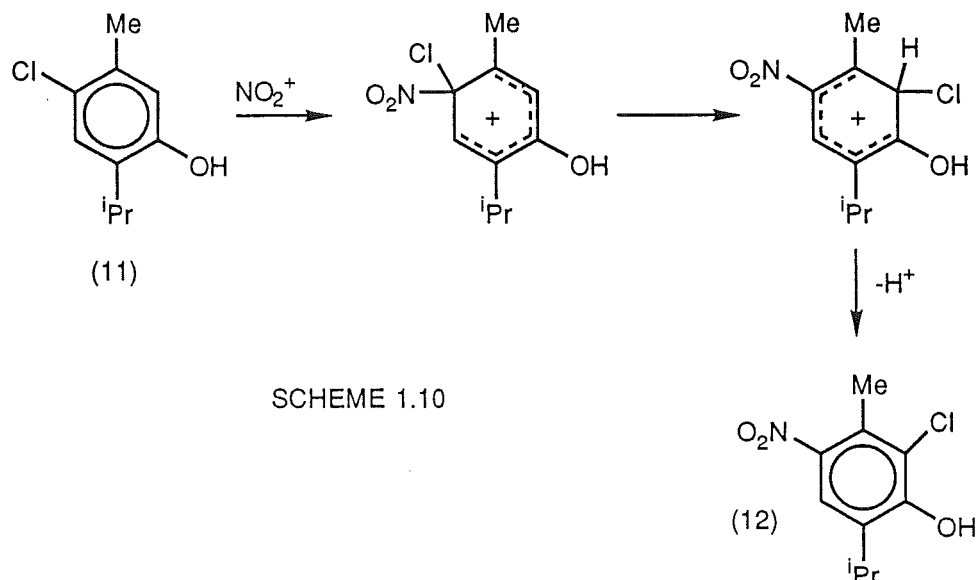
1.2.4 Substituent Migration

Migration within the Wheland intermediate to relieve the cationic charge can occur by movement of either the *ipso* substituent or the electrophile. Evidence of movement of the electrophile demands observation of the intermediate formed in the initial attack. One such example exists in the nitration of 2,6-dibromo-4-methylphenol (7) (Scheme 1.9).¹¹ Addition of nitrogen dioxide to a solution of the phenol resulted in the formation of a single product (10). At first it was thought to arise from simple electrophilic substitution of a bromine, but it was demonstrated that the reaction occurs through the 4-nitro dienone (8), followed by a 1,3 migration of the nitro group and loss of a bromine.



An example of migration of the *ipso* substituent was documented in the nitration of 6-chlorothymol (11) (Scheme 1.10, over).¹² The action of nitric acid on a solution of the thymol yielded pure 2-chloro-6-nitrothymol (12).

As shown below, this product arises from electrophilic attack *ipso* to the chlorine, followed by a 1,3-chlorine migration and proton loss. In this case the likely mechanism is evident from inspection of the structures of the substrate and product.



SCHEME 1.10

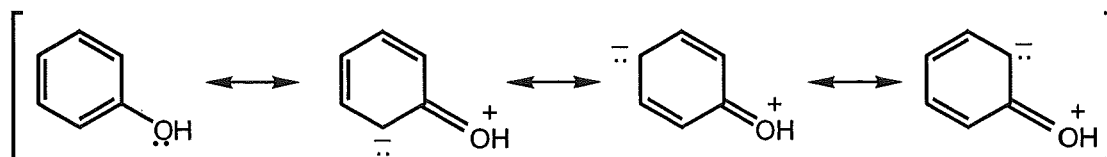
1.3 Electrophilic Attack of Phenols:

The addition of a hydroxyl group to the aromatic ring has a marked affect on the reactivity of the system. Reviews by Ershov *et al.* and Brittain and de la Mare cover a wide aspect of the chemistry of these compounds.^{13,14} Due to the electron donating character of the O-H the aromatic ring is enhanced towards electrophilic attack in relation to benzene. The relative rates of nitration of various aromatic compounds with nitric acid are given as examples in Table 1.1.¹⁵

Table 1.1 Relative Rates of Nitration

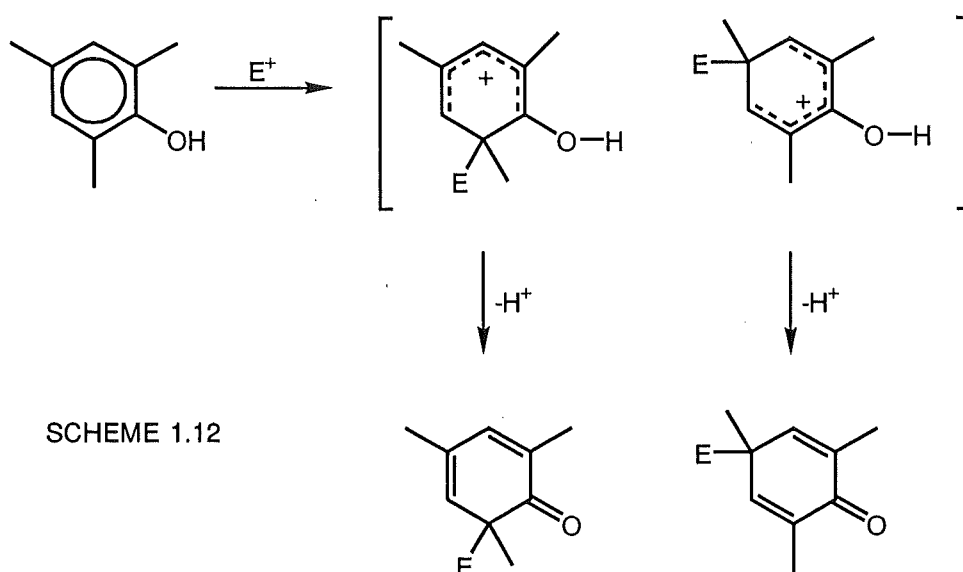
Compound	k_{rel}
Benzene	1
Toluene	25
Phenol	1000
Chlorobenzene	0.03
Nitrobenzene	6×10^{-8}

For phenols, the *ortho* and *para* positions are favoured over the *meta* positions for electrophilic attack due to delocalisation of the oxygen lone pairs into the ring (Scheme 1.11).



SCHEME 1.11

In the course of this work all phenols examined were substituted in both *ortho* and the *para* position, by either a halogen or a methyl group, neither of which are stable as leaving groups. This reduces the likelihood of substitution. Instead the neutralisation of the positive charge comes from a side-chain modification. Loss of the hydroxy proton, and the subsequent generation of a dienone system occurs rapidly. Depending upon the site of the electrophilic attack either a linearly conjugated cyclohexa-2,4-dienone or a cross-conjugated cyclohexa-2,5-dienone system is formed (Scheme 1.12).

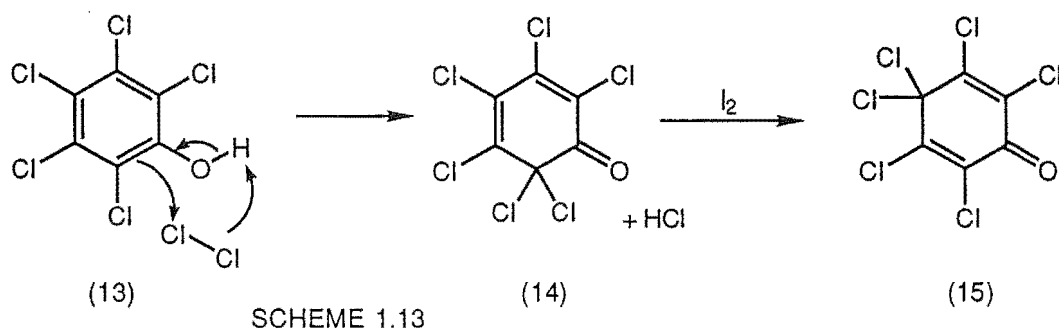


SCHEME 1.12

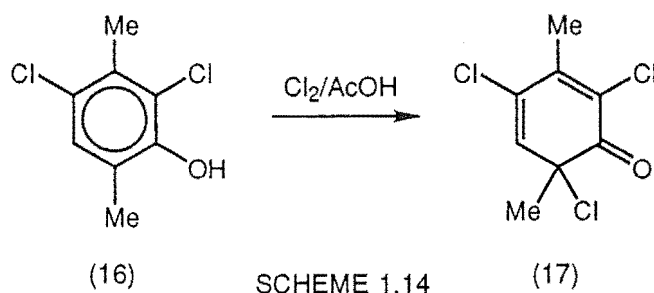
cyclohexa-2,4-dienone cyclohexa-2,5-dienone

Reactions of phenols with molecular chlorine in non-polar solvents give a cyclohexa-2,4-dienone system initially but these may isomerise to the

corresponding cyclohexa-2,5-dienones under certain conditions. Dennivelle and Fort proposed the following mechanism to account for the exclusive *ortho* position of this initial attack (Scheme 1.13).¹⁶ A concerted abstraction of the phenolic proton from pentachlorophenol (13) and attack of Cl^+ does not occur at the *para* position.

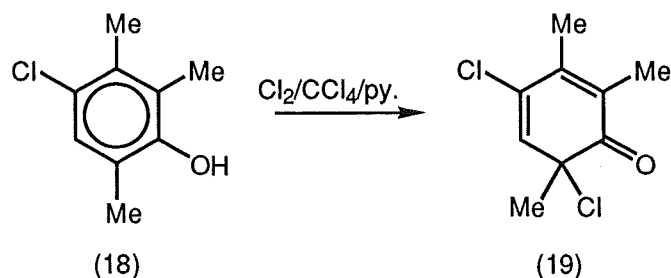


In dienones with chlorine at C4 the linearly conjugated cyclohexa-2,4-dienone system is stable and will not spontaneously isomerise to the cyclohexa-2,5-dienone (15). In the above example of pentachlorophenol (13) isomerisation was effected on storage of the dienone in the presence of iodine.¹⁶ Volbracht and co-workers demonstrated the formation of a 6-chlorocyclohexa-2,4-dienone (17) from 2,4-dichloro-3,6-dimethylphenol (16). The corresponding 4-chlorocyclohexa-2,5-dienone was not observed.¹⁷



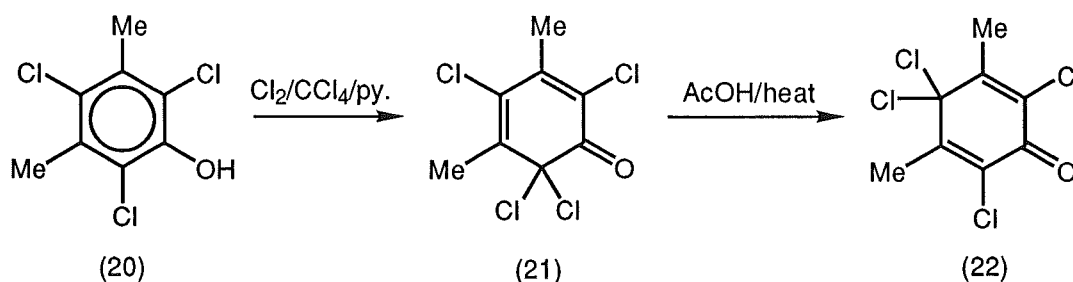
Morita and Dietrich chlorinated a wide variety of alkyl substituted 4-chlorophenols and nearly all gave 6-chlorocyclohexa-2,4-dienones.¹⁸ For example, reaction of 4-chloro-2,3,6-trimethylphenol (18) with chlorine in carbon tetrachloride in the presence of pyridine gave 2,4-dichloro-2,3,6-trimethyl-

cyclohexa-2,4-dienone (19) (Scheme 1.15).



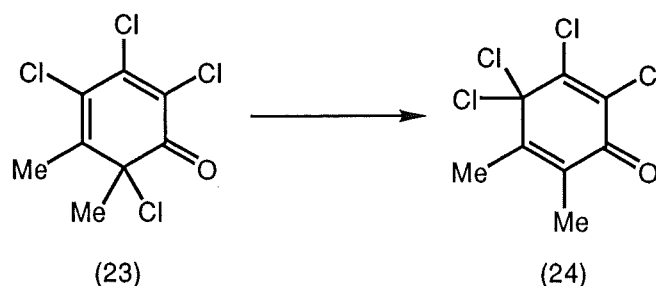
SCHEME 1.15

These workers found that the formation of 4,4-dichlorocyclohexa-2,5-dienones was rare. One example occurred in the reaction of 2,4,6-trichloro-3,5-dimethylphenol (20), as shown below (Scheme 1.16). This gave 2,4,6,6-tetrachloro-3,5-dimethylcyclohexa-2,4-dienone (21) as the product but isomerisation to 2,4,4,6-tetrachloro-3,5-dimethylcyclohexa-2,5-dienone (22) was observed upon heating in acetic acid.



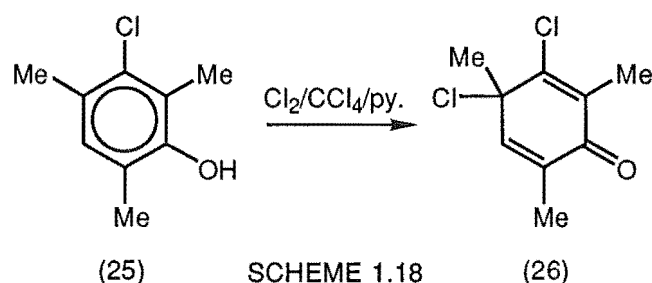
SCHEME 1.16

Another cyclohexa-2,4-dienone which isomerised was 2,3,4,6-tetrachloro-5,6-dimethylcyclohexa-2,4-dienone (23) (Scheme 1.17). This compound slowly transformed into the corresponding 2,5-dienone (24) on standing at room temperature.

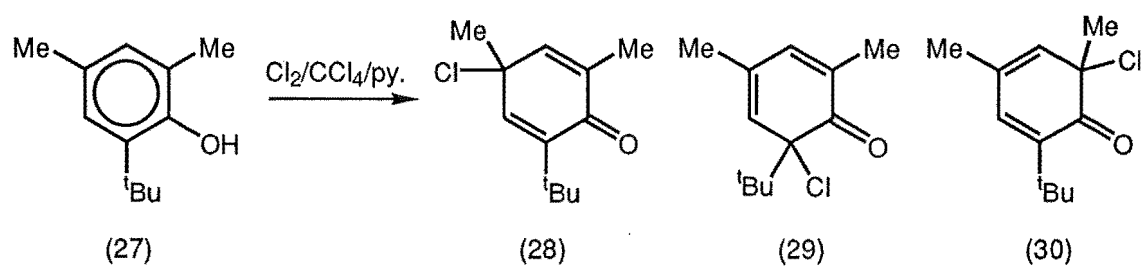


SCHEME 1.17

Isolation of 6-chlorocyclohexa-2,4-dienones from the chlorination of 4-alkyl substituted phenols is rare, with isomerisation to the 4-chlorocyclohexa-2,5-dienone being rapid. Fischer and Henderson reported the chlorination of a variety of 4-alkylphenols in acetic anhydride which all gave 4-alkyl-4-chlorocyclohexa-2,5-dienones.¹⁹ Even with bulky 4-alkyl substituents such as isopropyl and *tert*-butyl no cyclohexa-2,4-dienones were observed. Studies of the chlorination of various substituted 2,4-dimethylphenols by Morgan showed that only 2,5-dienones were stable under the reaction conditions.²⁰ For example, chlorination of 3-chloro-2,4,6-trimethylphenol (25) in carbon tetrachloride in the presence of pyridine gave 3,4-dichloro-2,4,6-trimethylcyclohexa-2,5-dienone (26) in quantitative yield (Scheme 1.18).



Judd reported the formation of a mixture of cyclohexa-2,4-dienones (29), (30) and a cyclohexa-2,5-dienone (28) arising from the chlorination of 2-*t*-butyl-4,6-dimethylphenol (27) in carbon tetrachloride in the presence of pyridine (Scheme 1.19).²¹ However in D_3 -chloroform solution the 6-chlorocyclohexa-2,4-dienone components isomerised to yield a solution of the 4-chlorocyclohexa-2,5-dienone (28).

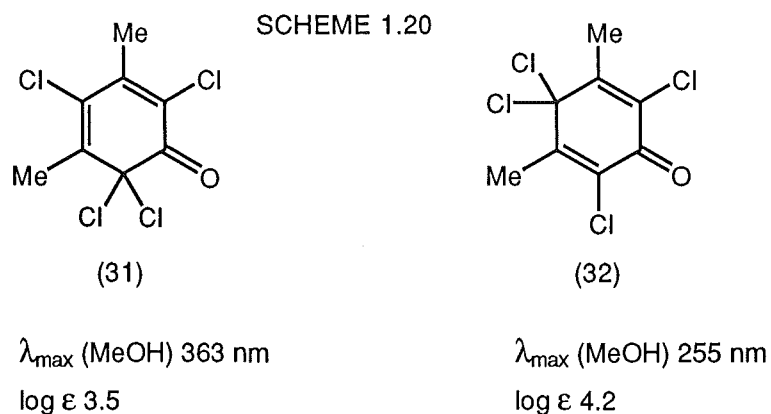


SCHEME 1.19

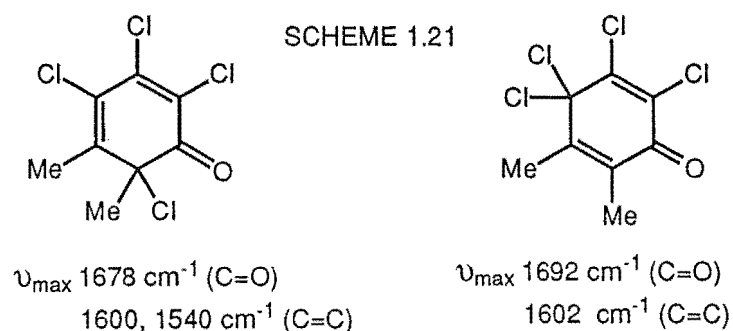
5 : 4 : 7

During the course of this work a variety of 4-chlorophenols were chlorinated and only 6-chlorocyclohexa-2,4-dienones were observed.

6-Chlorocyclohexa-2,4-dienones can be readily distinguished from their 2,5-isomers by a variety of spectroscopic techniques. The linearly conjugated 2,4-dienone system displays a π - π^* transition in the ultraviolet region with typical values of λ_{\max} in the region 290 to 340 nm. The absorptions are of moderate intensity, normal $\log \epsilon$ values range from 3.2 to 3.8. In comparison the same transition in 4-chlorocyclohexa-2,5-dienone systems occurs at shorter wavelengths and is generally of greater intensity, typically λ_{\max} falls in 220-250 nm region and $\log \epsilon$ values 3.9 to 4.5 are commonplace. For example, Morita and Dietrich found the following values for the two dienones (31) and (32) (Scheme 1.20).¹⁸



Both carbonyl and olefinic vibrations in the infrared region can be used for assignment of dienones. The cyclohexa-2,5-dienones usually exhibit the carbonyl stretch at a higher frequency than the 2,4-isomers, but exceptions are common because of substituents effects. The asymmetric cyclohexa-2,4-dienone displays two olefinic absorption bands, whereas only one is usually seen for the 2,5-dienone. For example, the values for the two cyclohexadienones shown over (Scheme 1.21) are typical for both 2,4- and 2,5-dienones.¹⁸



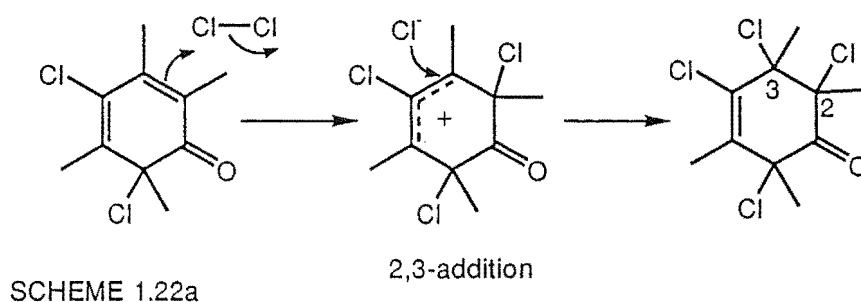
The two dienone systems can also be differentiated by the ^{13}C n.m.r. resonance of the carbonyl carbon.²² The signal for a 2,4-dienone carbonyl carbon lies downfield from δ 190, while for cyclohexa-2,5-dienones this signal occurs upfield of that position.

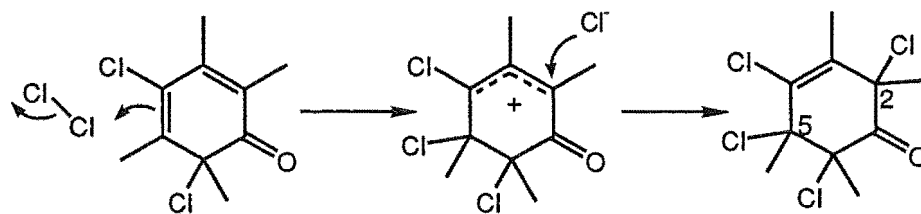
1.4 Further Addition of Chlorine to 2,4-Dienones

6-Chlorocyclohexa-2,4-dienones may add further chlorine to the diene system to give monounsaturated ketones. This addition can occur by several routes, which can be grouped according to the behaviour of the attacking chlorine - either electrophilic or nucleophilic in character.

1.4.1 Electrophilic Addition

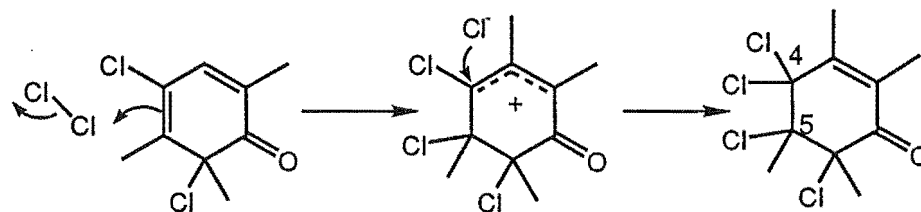
Chlorine can add to the π -system of the cyclohexa-2,4-dienone to give a delocalised cationic intermediate which is captured by chloride ion to generate the enone. The chlorine can add in three patterns - 2,3-addition, 2,5-addition or 4,5-addition. In all these cases the chlorine is electrophilic in character.





SCHEME 1.22b

2,5-addition

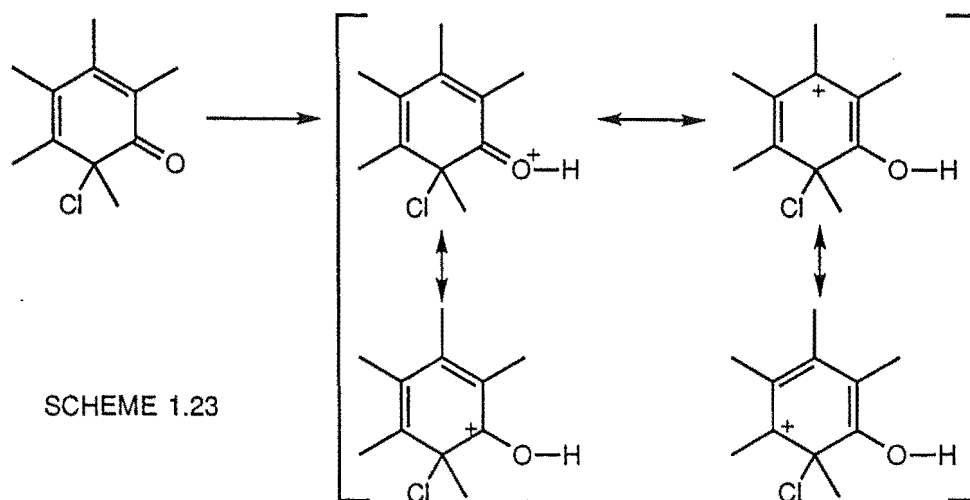


SCHEME 1.22c

4,5-addition

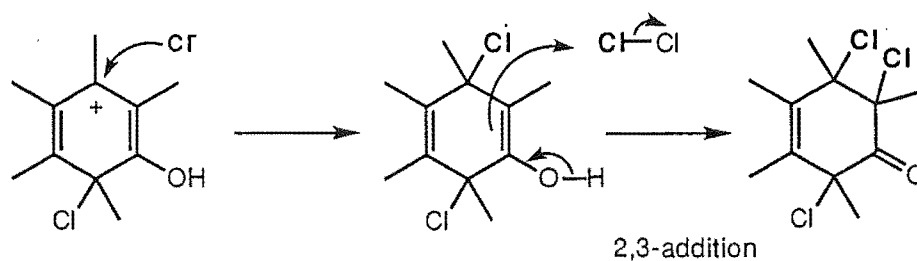
1.4.2 Nucleophilic Attack

The carbonyl group deactivates the olefinic system for electrophilic attack and electron withdrawing substituents on the ring increase this affect. Under these circumstances an alternative mode of chlorine addition can occur. The mechanism of this route is not fully understood but is known to involve a pre-equilibrium protonation of the carbonyl group²³ and is powerfully catalysed by hydrogen chloride. For example, the rate of reaction of trans-cinnamaldehyde with chlorine was increased from 3.42 to 55.7 l mol⁻¹ sec⁻¹ when hydrogen chloride was added at a concentration of 0.025 mol l⁻¹.²³ The presence of a species to remove hydrogen chloride will inhibit reaction by this pathway. R. J. Martyn proposed the following mechanism (Scheme 1.23) to account for the above observations.²⁵

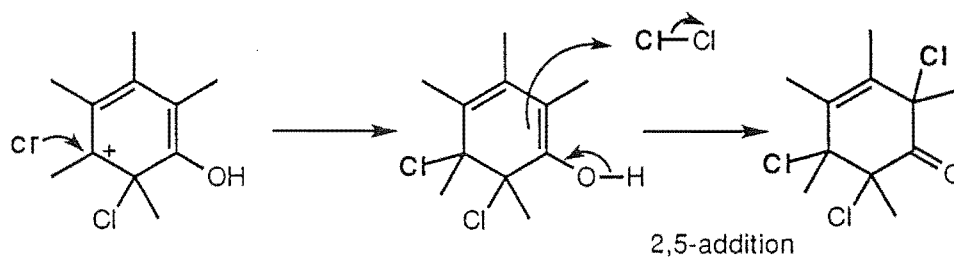


SCHEME 1.23

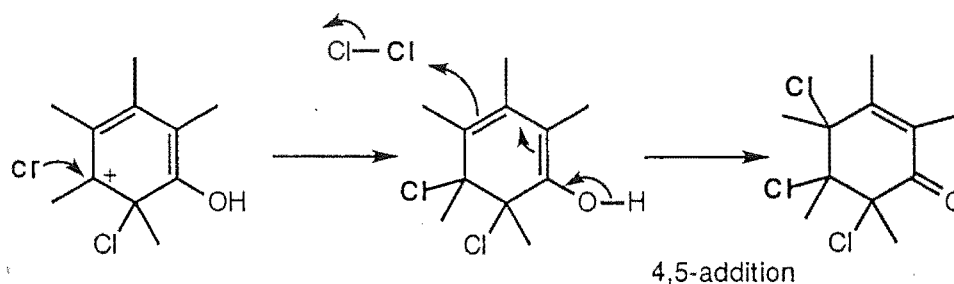
Attack by chloride ion at the site of the positive charge (either C3 or C5) generates a reactive enol moiety, which is rapidly attacked by chlorine to regenerate the hydrogen chloride catalyst and giving the monounsaturated ketone (Scheme 1.24).



SCHEME 1.24a

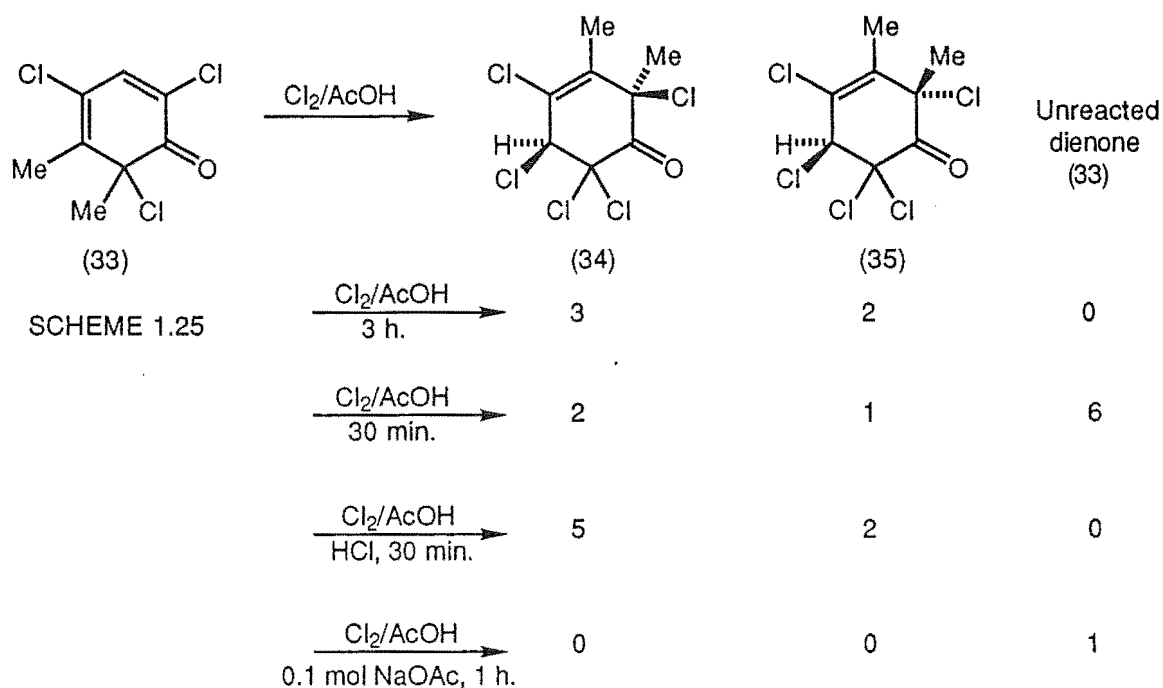


SCHEME 1.24b

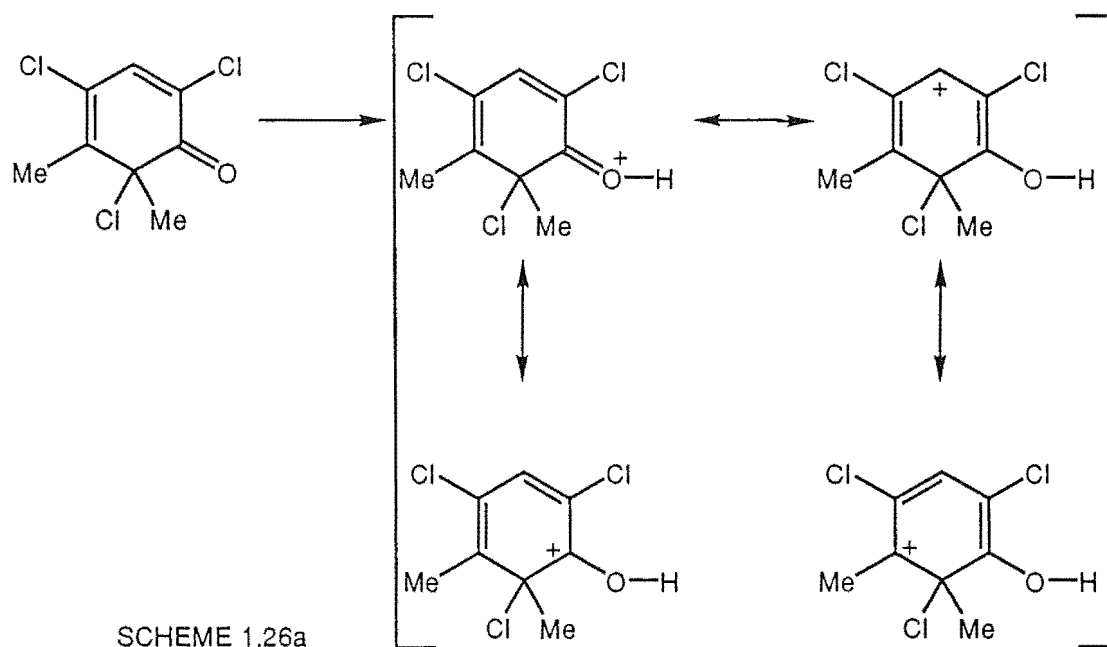


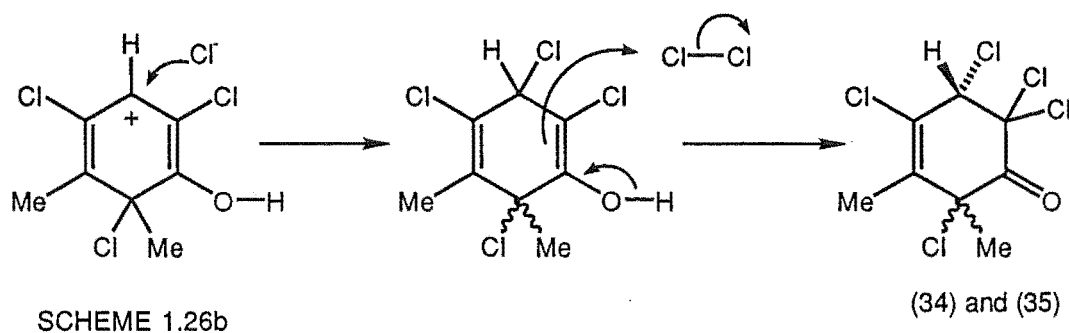
SCHEME 1.24c

An example of reaction by nucleophilic pathways occurred in the chlorination of 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) in acetic acid (Scheme 1.25, over), where the reaction was accelerated by addition of hydrogen chloride and effectively halted by addition of sodium acetate.²⁵



According to the above mechanism (Scheme 1.23 and 1.24), reaction would occur with initial protonation of the carbonyl oxygen (Scheme 1.26a). Attack by chloride ion at C3, with subsequent proton loss and chlorine addition generates the two pentachloro ketones (34) and (35) (Scheme 1.26b, over). It is worth noting in this example the steric influences of the substituents play a vital role in the course of the reaction. Instead of attack at the more stable and longer lived tertiary C5 carbocation, chloride ion attacks at the less hindered C3 site.





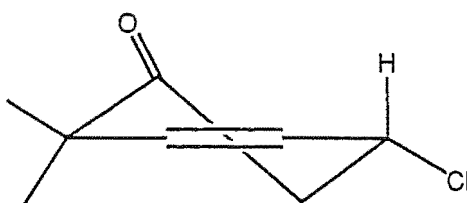
During the course of this work suppression of nucleophilic addition was achieved by the use of acetic anhydride as a solvent. In the study of the mechanism of the HCl-catalysed acylation of β -naphthol by carboxylic anhydrides Satchell demonstrated that the reaction involved reaction of hydrogen chloride and acetic anhydride to form acetic acid and acetyl chloride which acted as the acylating agent.²⁶ It is believed that this reaction prevents nucleophilic addition, by removal of hydrogen chloride.

Work to date indicates several aspects about this mode of reaction. It appears that a 2,4-dichloro moiety is a prerequisite for reaction by nucleophilic pathways. Although attack at C3 is well documented, there are no examples of nucleophilic attack at C5 of a 4,6-dichloro-6-methylcyclohex-2,4-dienone. This may be the result of insufficient activation towards nucleophilic attack due to the C4-Cl and the Cl-C6-Me substituents.

1.5 Conformation of Polychlorocyclohex-3-enones and Polychlorocyclohex-2-enones:

1.5.1 Polychlorocyclohex-3-enones

An analysis of ^1H n.m.r., ultraviolet and infrared spectroscopic data of a large series of polychlorocyclohex-3-enones by Morita and Dietrich led them to the conclusion that the conformation of the alicyclic ring was a modified half-chair with the C5 hydrogen *pseudo*-axial.¹⁷ This constrained the C5 chlorine to a *pseudo*-equatorial position.



This conformation was later shown to be incorrect by Hartshorn and co-workers²⁹, and that the ring actually exists in a skew-boat conformation. This was demonstrated for the solid state by X-ray crystal structures and infrared spectroscopy, and in solution by ^1H n.m.r. data, for a series of polychlorocyclohex-3-enones with H (Cl) C5, Me (Cl) C5 and Cl (Cl) C5 features. The chlorine occupies the flagpole orientation of the skew-boat, the torsion angle for the C5 chlorine (C(3) - C(4) - C(5) - Cl(5)) was found to be $89(1)^\circ$ in the X-ray crystal structure of the polychlorocyclohex-3-enone (36) reported by Martyn.²⁵

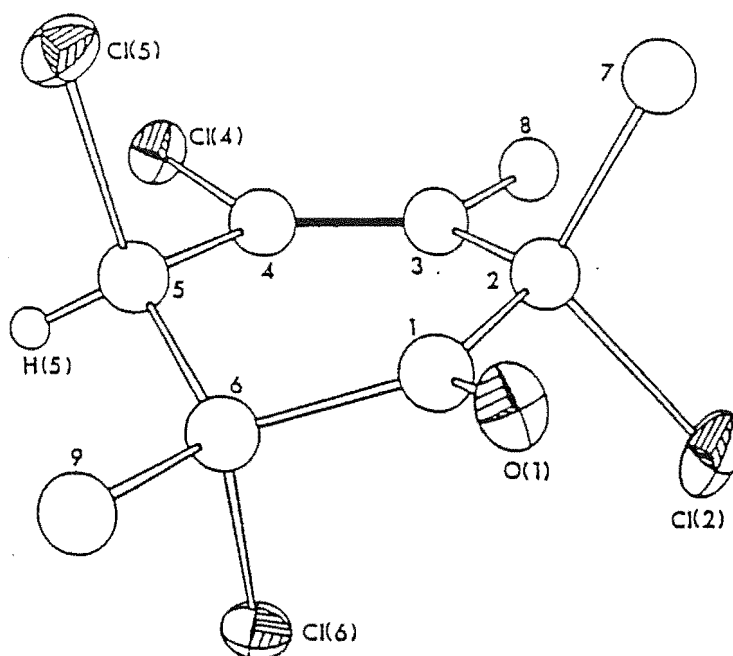
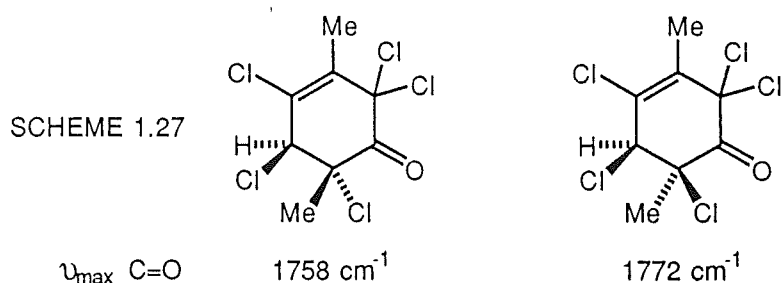


Figure 1.1 Perspective Drawing of (36), Ellipsoids are at 50% probability level.
Double bonds are shown in black.

The geometry around C6 is similar to the α -carbon of a chair cyclohexanone^{27,28} and the C6 substituents occupy the axial and equatorial

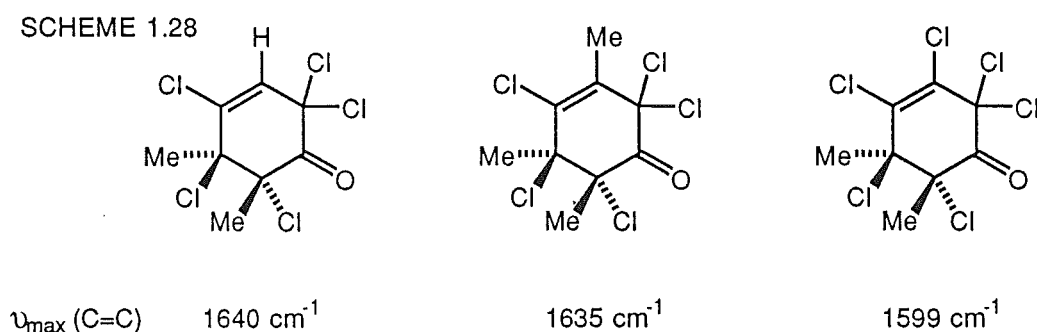
positions, O(1)-C(1)-C(6)-C(9) $-9(1)^\circ$ and O(1)-C(1)-C(6)-Cl(6) $108.5(9)^\circ$. Due to the sp^2 character of both C1 and C3 the torsion angles for the substituents on C2 are of a more similar magnitude, O(1)-C(1)-C(2)-Cl(2) $73(1)^\circ$ and O(1)-C(1)-C(2)-C(7) $-44(1)^\circ$.

A great deal of information concerning the stereochemistry of the substituents can be extracted from spectroscopic data. The effect on the carbonyl absorption in the infrared spectrum on reversing the positions of a methyl group and a chlorine on C2 is small due to similarities in the torsion angles of the two positions i.e. C2 epimers will display near identical ν_{\max} (C=O) values. For example the polychlorocyclohex-3-enone (36) shown above, and the corresponding C2 epimer both display ν_{\max} (C=O) at 1750 cm^{-1} .²⁹ However, due to large differences in torsion angles for the C6 substituents (-9° c.f. 108.5°) inversion of stereochemistry at this site has a marked affect on the position of the absorption maximum. A polychlorocyclohex-3-enone with an equatorial methyl group and an axial chlorine at C6 will display ν_{\max} (C=O) up to 20 cm^{-1} lower than the corresponding epimer. This results from dipole-dipole interactions which are introduced when the chlorine substituent is close to co-planar with the carbonyl group. An example of this effect is shown in Scheme 1.27.²⁹

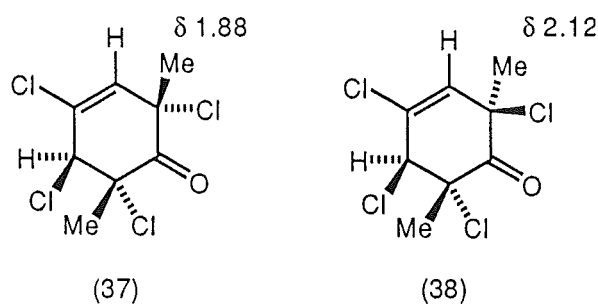


The olefinic vibration is affected by both C3 and C4 substituents but during the course of this work the C4 substituent was limited to chlorine. In this context, the frequency of the absorption is dependant upon the nature of the C3 substituent. When comparing methyl and chlorine substituents at C3

the ν_{\max} (C=C) will occur about 20 cm^{-1} higher for the former. This trend is illustrated in the series^{18,25}, as shown in Scheme 1.28.

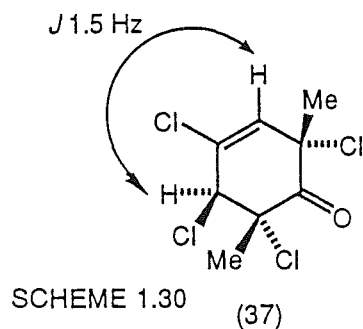


The ^1H n.m.r. signals of ring substituents can provide information about the stereochemistry of polychlorocyclohex-3-enones. It has been demonstrated in 5α -steroids that the $(\text{H}19)_3$ methyl protons are deshielded by a 1,3-syn-axial interaction with a chloro substituent across the ring.^{27,28} This results in the ^1H n.m.r. signal moving downfield by δ 0.32. In polychlorocyclohex-3-enones the possibility of this type of interaction exists from C2 to C6 but as the distance is larger than in the steroid model the magnitude of the deshielding effect is less. For example, the C6 chlorine deshields the C2 methyl group in the trans isomer (38) to the extent of δ 0.24 (Scheme 1.29).



SCHEME 1.29

^1H - ^1H coupling through the olefinic system has been observed for polychlorocyclohex-3-enones with protons at C3 and C5. This type of allylic coupling is small, typically less than 3 Hz. An example of this was observed in the polychlorocyclohex-3-enone (37) shown over in Scheme 1.30.³⁰



1.5.2 Polychlorocyclohex-2-enones

In the solid state the ring adopts a flattened half-chair conformation. A typical example is the polychlorocyclohex-2-enone (39) shown below.²³

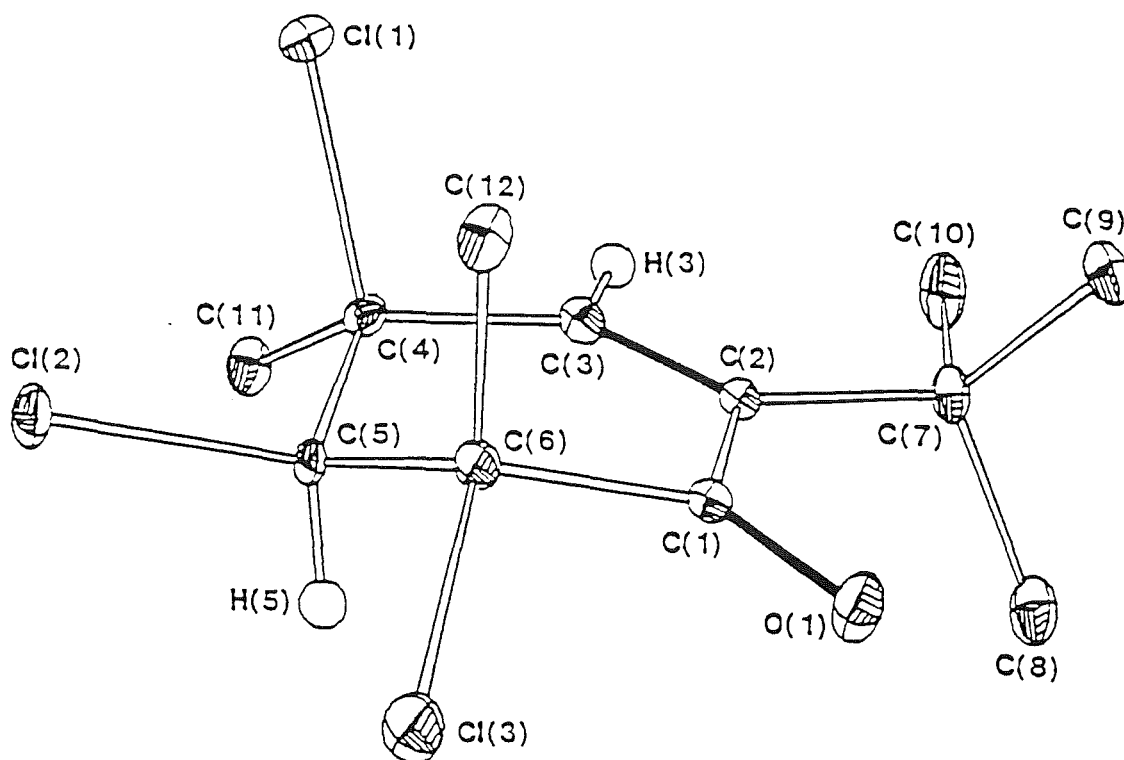
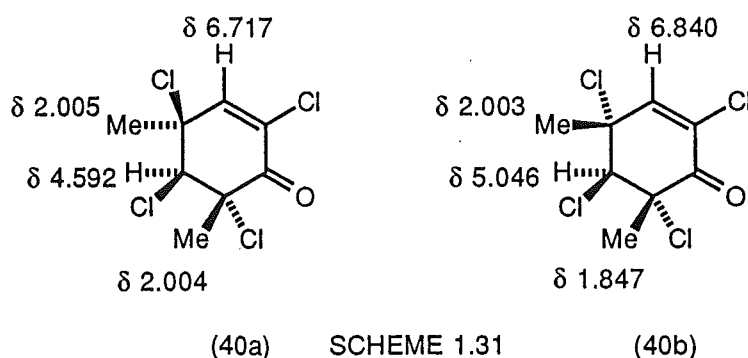


Figure 1.2 Perspective Drawing of (39). Ellipsoids are at 20% probability level.

Double bonds are shown in black.

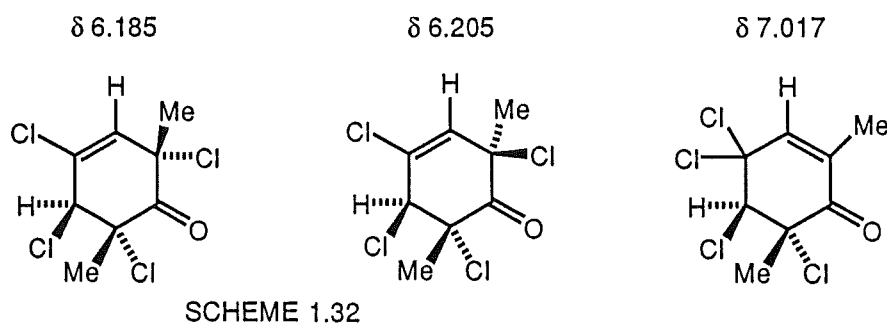
The torsional angles $C(2)-C(3)-C(4)-C(5)$ $-13.2(4)^\circ$ and $C(6)-C(1)-C(2)-C(3)$ $-11.0(4)^\circ$ are indicative of this alicyclic ring conformation. The orientation of the chlorine on C4 is *pseudo*-axial ($H(3)-C(3)-C(4)-Cl(1)$ $-72.4(2)^\circ$) and the methyl group is *pseudo*-equatorial ($H(3)-C(3)-C(4)-C(11)$ $-41.7(3)^\circ$). Inversion of stereochemistry at this centre affects the 1H n.m.r. shift of other protons

in the molecule. For example, A. J. Morgan found the following values for compounds (40a) and (40b) (Scheme 1.31).²⁰



In compound (40b) the *pseudo*-equatorial C4-chlorine is in a position to deshield H3 (by δ 0.123) and H5 (by δ 0.454) but does not affect the C6-methyl group. Inversion at C4 eliminates the shifts above, but brings about a 1,3-diaxial interaction between the C4-chlorine and the C6-methyl group resulting in the 6-Me ¹H n.m.r. signal shifting downfield by δ 0.177

Finally, the carbonyl group of a conjugated polychlorocyclohex-2-enone is known to decrease the electron density in the carbon-carbon double bond, this effect being greater at the β-carbon, but does not occur for polychlorocyclohex-3-enones.³¹ This difference is made apparent in the ¹H n.m.r. shift of H3, and can be large. A typical example is shown below (Scheme 1.32).³⁰



1.6 Interconversion of Cyclohexa-2,4-dienones

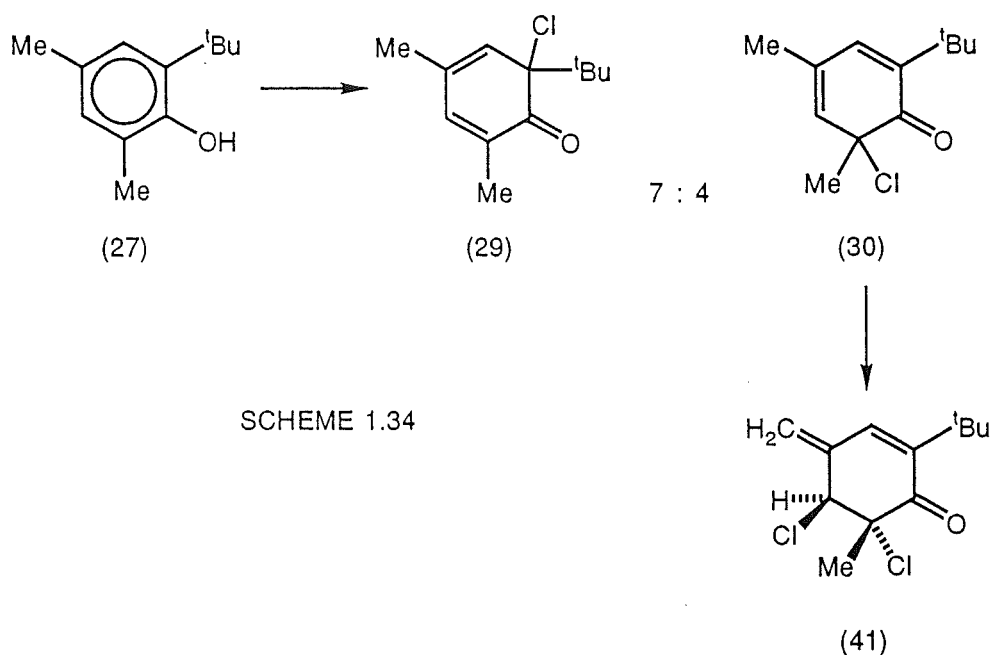
The interconversion of polyenes by sigmatropic rearrangement has attracted both experimental and theoretical interest. The simplest rearrangement of

this type that can be readily observed is the [1,5]-hydrogen transfer in *cis*-1,3-pentadiene, as shown in Scheme 1.33.³²

SCHEME 1.33

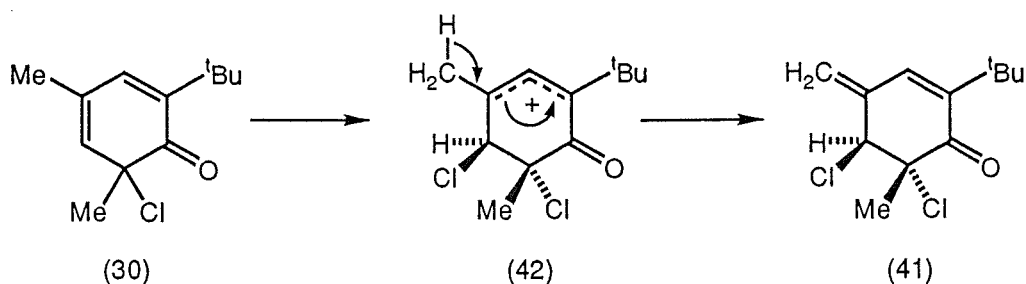


Activation energies for this transfer using deuterium labelling were reported for the gas phase as being *ca.* 8 kJ mol⁻¹.³³ The transition structure for the interconversion has been well studied by theoretical methods.^{32,34,35} This type of tautomerism is known for cyclohexa-2,4-dienones with migrating species such as bromine³⁶, phenoxy³⁷ and nitro groups.³⁸ 6-Chlorocyclohexa-2,4-dienones also undergo this rearrangement. Judd demonstrated that the inseparable mixture (c. 7 : 4) of the two 6-chlorocyclohexa-2,4-dienones (29) and (30) reacted with chlorine to give a single product (41) (Scheme 1.34).²⁰



SCHEME 1.34

The product is formed from the minor dienone (30) by attack of chlorine at C5 giving the delocalised cation (42) shown over (Scheme 1.35). Elimination of a proton from the methyl group yielded the exocyclic methylene group.



SCHEME 1.35

This is supported by the expectation that for the major dienone chlorine attack at C5 adjacent to the bulky *tert*-butyl group would be a relatively slow process and a [1,5]-sigmatropic shift of chlorine would give the dienone (30) which will react further. This rationalisation is consistent with the absence of dienone (29) or any products arising from it, at the end of the reaction.

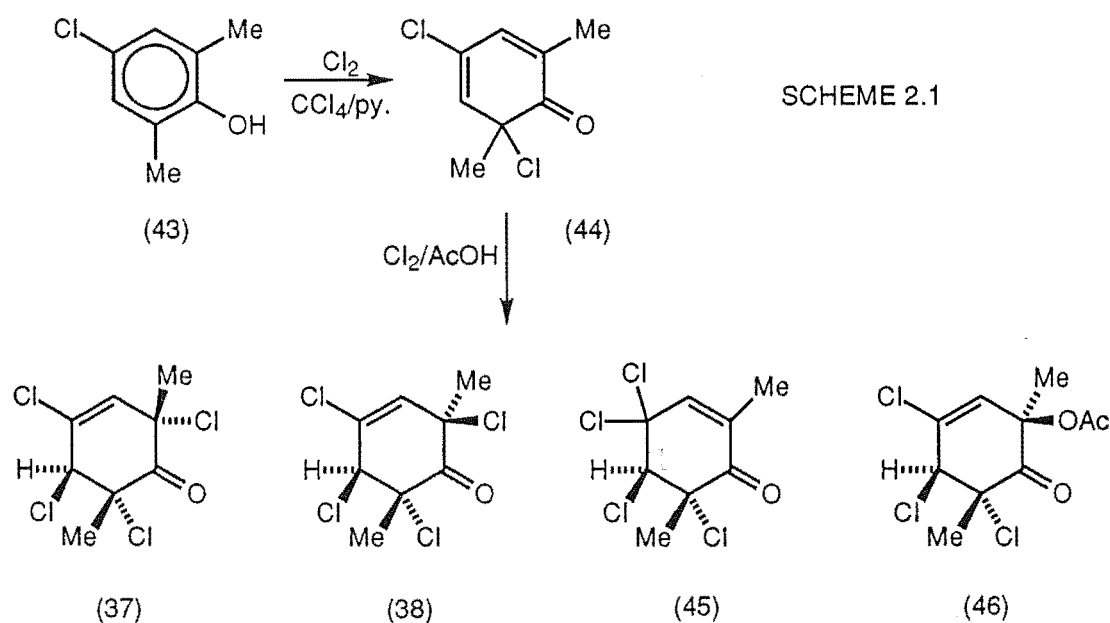
This thesis is concerned with the study of the chlorination reaction of a series of 4-chloro-6-methylphenols with either chlorine or methyl groups at other positions on the ring. Particular attention is paid to the stereochemistry of the chlorine addition. In the course of this study we wished to explore what affect the positioning of either an electron donating methyl group, or an electron withdrawing chlorine would have on the pathway by which these phenols reacted. Included in this work is a brief investigation of the [1,5]-sigmatropic shift of chlorine in various cyclohexa-2,4-dienones by experimental and theoretical techniques.

CHAPTER TWO

CHLORINATION OF SUBSTITUTED 2,6-DIMETHYLPHENOLS

2.1 The Chlorination Reactions of 4-Chloro-2,6-dimethylphenol (43):

The formation of 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) was effected by addition of chlorine (1.2 mole equivalents) to a solution of the phenol (43) in carbon tetrachloride containing pyridine. Light was excluded from the flask to eliminate free radical side-chain chlorination. (Detailed reaction conditions are set out in the experimental section relating to Chapter 2.) This reaction gave a single product which was shown to be essentially pure dichloro dienone (44), identical with authentic material (Scheme 2.1).¹⁸



2.1.1 Reaction of Chlorine with 4,6-Dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) in Acetic Acid

Reaction of the dichloro dienone (44) with chlorine in acetic acid gave a mixture of four compounds (Scheme 2.1) which were separated by chromatography. The tetrachloro ketones (37) (13%) and (38) (40%) were eluted first, and

identified by comparison with authentic material.³⁹ Eluted next was the 4,4,5,6-tetrachlorocyclohex-2-enone (45) (31%), the structure of which was assigned on the basis of its elemental analysis and spectroscopic data. The ultraviolet and infrared spectra indicated the presence of a conjugated ketone (ν_{\max} 1704 cm^{-1} ; λ_{\max} 232 nm, ϵ 7850). Allylic coupling in the ^1H n.m.r. spectrum [from H3 (δ 7.017) to the C2-methyl protons (δ 1.988) J 1.45 Hz], which would be absent in a non-conjugated ketone also supports the proposed structure. The H5 signal (δ 5.015) is moderately far downfield for a proton *ipso* to a chlorine atom (c.f. (40) and (41), Scheme 1.31, p. 22) which is indicative of the presence of two chloro substituents at C4 in the structure. The C2-methyl signal is in an upfield position in the absence of a chlorine substituent at C3. The ^{13}C n.m.r. is in accord with the proposed structure. There is no direct evidence for the *trans*-5,6-dichloro stereochemistry but this assignment is made on the basis of the parallel formation of the tetrachloro ketones (37) and (38), and the trichloro acetate (46) (see below), each of which has the *trans*-5,6-dichloro arrangement. The final component of the mixture was identified as the trichloro acetate (46) (16%), identical with authentic material.²⁵

2.1.2 Reaction of Chlorine with 4,6-Dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) in Acetic Acid containing Sodium Acetate

Reaction of the dichloro dienone (44) with chlorine in acetic acid with added sodium acetate gave only three of the above products. The yield of the *cis*-2,5-dichloro compound (38) was not significantly altered (43%), but the yield of the trichloro acetate (46) was increased (42%) at the expense of the 4,4,5,6-tetrachloro ketone (45) (15%). No *trans*-2,5-dichloro compound (37) was observed in the reaction mixture. The possibility existed that the 4,4,5,6-tetrachloro ketone (45) and the *trans*-2,5-dichloro compound (37) may be formed initially but under the reaction conditions might be converted into the

trichloro acetate (46). This was excluded by the observation that these compounds were stable under the reaction conditions.

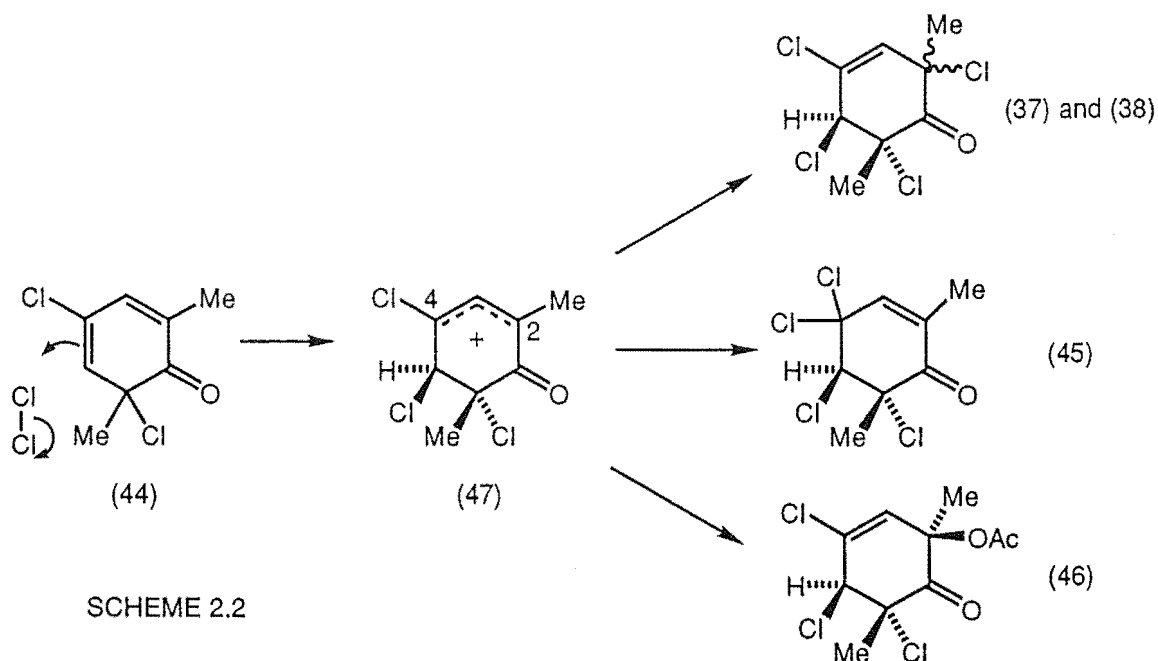
2.1.3 Reaction of Chlorine with 4,6-Dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) in Acetic Anhydride

Reaction of the dichloro dienone (44) in acetic anhydride gave all four products. The yield of the trichloro acetate (46) was similar (18%) to that obtained in acetic acid, but the percentage of *cis*-2,5-dichloro compound (38) was increased (59%). Again, the yields of both the *trans*-2,5-dichloro compound (37) and the 4,4,5,6-tetrachloro ketone (45) were reduced (8% and 15% respectively).

2.1.4 Discussion

The observation that the reactions in acetic anhydride and in acetic acid with added sodium acetate are not retarded indicates the reactions with the dichloro dienone (44) are electrophilic in nature.

The above results are consistent with initial electrophilic attack of chlorine at C5 of the dichloro dienone (44) to give the delocalised cation (47) (Scheme 2.2).



Capture of the cation at C2 by chloride ion would give the two tetrachlorocyclohex-3-enones (37) and (38); at C4 by chloride ion would give the 4,4,5,6-tetrachloro ketone (45); and at C2 by either acetic acid or acetate ion would give the trichloro acetate (46).

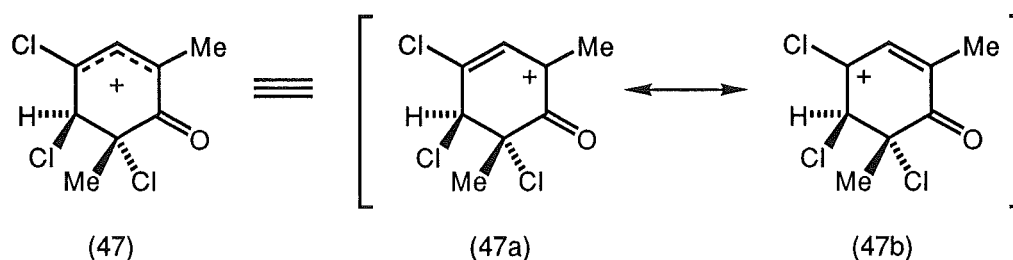
Capture of the cation (47) at C2 by chloride ion will occur rapidly in the *cis* arrangement as the chloride ion is formed close to the newly formed cationic system, and on the same face as the first chlorine to add to the π -system. *Trans*-2,5-addition requires migration of free chloride ion to the opposite face of the ring. In acetic acid this migration does occur, but this is not a favourable process, as shown by the low yield of the *trans*-2,5-dichloro compound (37) (13%). In solvent systems which can remove chloride ion the migration will not occur to as great an extent, and the yield of the *trans*-2,5-dichloro compound (37) will be reduced. For example, in acetic acid with added sodium acetate no *trans*-2,5-addition was observed, and in acetic anhydride the yield of the *trans*-2,5-dichloro ketone (37) was only 8%. Correspondingly, the yield of *cis*-2,5-addition is increased in reactions in these solvent systems.

The reaction in acetic acid with added sodium acetate differs markedly from the reactions in acetic acid and in acetic anhydride in two ways. Firstly, the complete suppression of the formation of the *trans*-2,5-dichloro compound (37) indicates that sodium acetate is more effective at trapping chloride ion than acetic anhydride, where at least 8% of the total yield was formed *via* a free chloride ion migration. Secondly, the yield of the trichloro acetate (46) is greatly enhanced in the reaction in acetic acid containing sodium acetate (42%) compared with reactions in acetic acid (16%) and acetic anhydride (18%). This reflects the levels of free acetate ion the reaction as a competing nucleophile.

The reduced yield for the 4,4,5,6-tetrachloro ketone (45) in reactions in acetic acid with sodium acetate and in acetic anhydride may be rationalised if the

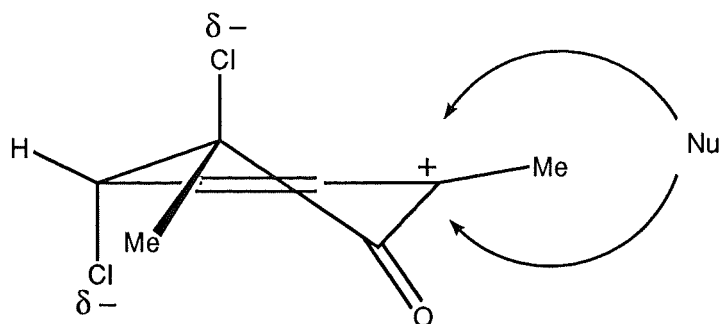
C4/C5-addition of chlorine occurs in a *trans* manner. This would require a free chloride ion migration, and as in the case of the *trans*-2,5-dichloro compound (37), the solvent would make this less favourable. However the *gem*-4,4-dichloro arrangement prevents any conclusions about the stereochemistry of the addition.

The generation of the trichloro acetate (46) with the *r*-2-acetoxy-*c*-5-chloro geometry is believed to occur due to the steric and electrostatic effects of the axial C6-chlorine influencing the incoming acetate group. Attack by chlorine on the dichloro dienone (44) would generate the delocalised cation (47) (Scheme 2.2, above), the canonical forms of which may be represented as in Scheme 2.3.



SCHEME 2.3

The electron donating character of the C2-methyl group should make the left hand canonical form (47a) more stable, and thus make C2 the preferred site for nucleophilic attack. From the perspective view of this cation (shown below) it can be seen that both the C5-chlorine and the C6-chlorine are in positions to affect the incoming nucleophile, by both steric interactions and by the nature of the dipole of the carbon-chlorine bond.

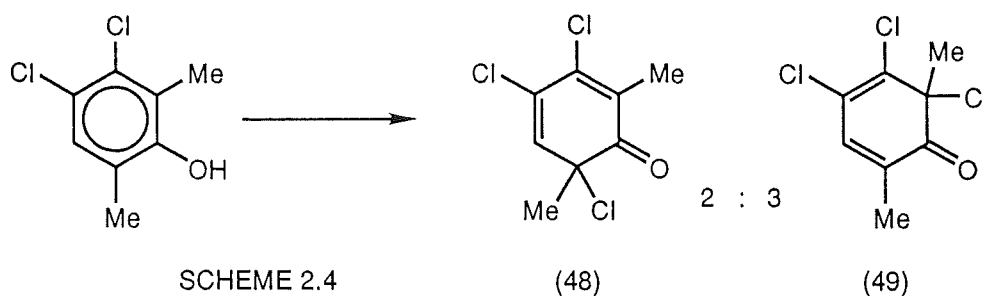


As the C6-chlorine is closer to C2, this substituent is believed to dictate the stereochemistry of the addition to C2. It is speculated that for these reasons acetate addition occurs exclusively *trans* to the C6-chlorine.

The *trans*-5,6-dichloro arrangement is believed to be favoured for electrostatic reasons. In the *cis* conformation the two chlorine substituents exist in a *gauche* configuration, and the dipole-dipole interaction makes this less favourable. Because the formation of the delocalised intermediate (47) (Scheme 2.2, above) requires a high energy of activation the transition state will occur late in the reaction coordinate.⁴⁰ This implies the transition state will closely resemble the cation (47) in character, and the formation of the *cis*-5,6-dichloro arrangement will be disfavoured at this point due to a higher energy intermediate and transition state.

2.2 The Chlorination Reactions of 3,4-Dichloro-2,6-dimethylphenol:

Conditions for the formation of the trichloro dienones were identical to those used for 4-chloro-2,6-dimethylphenol (Section 2.1). The reaction gave a mixture (*ca.* 2 : 3) of two isomeric 6-chlorocyclohexa-2,4-dienones (48) and (49) (Scheme 2.4), which could not be separated by chromatography.

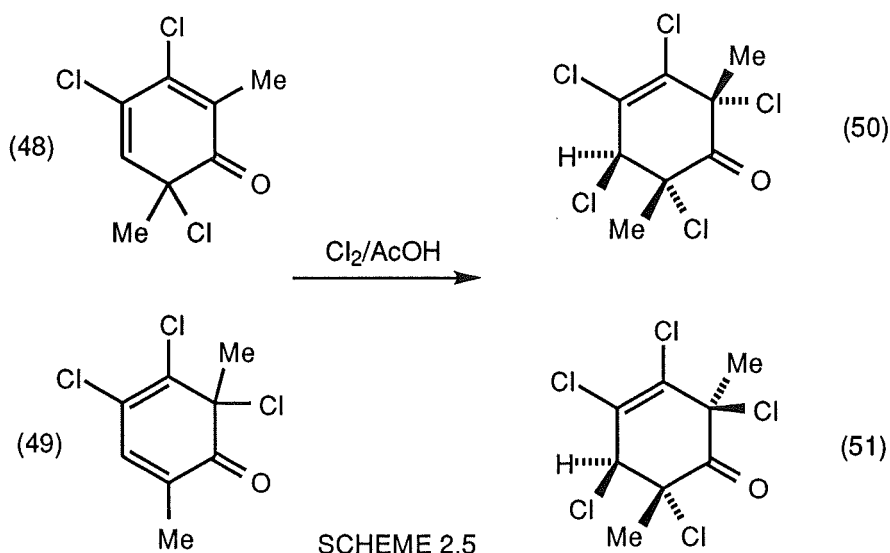


The components were identified by their ¹H n.m.r. spectra and results of nuclear Overhauser enhancement experiments. The 4,5,6-trichloro dienone (49) displays allylic coupling from H3 (δ 6.854) to the C2-methyl protons (δ 2.007) with *J* 1.5 Hz. A n.O.e. enhancement of 3% is seen at H3 on irradiation of the

C2-methyl protons and a 0.5% enhancement in the reverse direction. The coupling observed in the 3,4,6-trichloro dienone (48) occurs from H5 to the C2-methyl protons through the olefinic system and is of longer range, hence the reduced magnitude of the coupling constant (J 0.8 Hz). The methyl group assignment in the ^1H n.m.r. spectrum was confirmed by n.O.e. enhancements from C6-methyl protons to H5 (3%) and H5 to the C6-methyl protons (0.3%).

2.2.1 Reaction of Chlorine with a Mixture of 3,4,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) and 4,5,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) in Acetic Acid

Reaction of the two trichloro dienones (48) and (49) with chlorine in acetic acid gave a mixture of two pentachloro compounds, (50) and (51) (Scheme 2.5) (yields 46% and 54% respectively), which were separated by chromatography. Both of these were known compounds and their structures had been assigned earlier on the basis of their spectroscopic data.²⁹



The structure of compound (51) was confirmed by single crystal X-ray analysis. A perspective drawing of *r*-2,3,4,*c*-5,*t*-6-pentachloro-2,6-dimethylcyclohex-3-enone, $\text{C}_7\text{H}_8\text{Cl}_5\text{O}$, m.p. $124-126^\circ$ is presented in Figure 2.1 (over) with corresponding atomic coordinates in Table 6.1. In the solid state the alicyclic

ring of compound (51) exists in a flattened skew-boat conformation similar [torsion angles C(1)-C(2)-C(3)-C(4) 7.4(7)°; C(3)-C(4)-C(5)-C(6) -30.5(6)°; C(3)-C(4)-C(5)-Cl(5) 90.2(5)°] to analogous structures reported earlier.²⁹

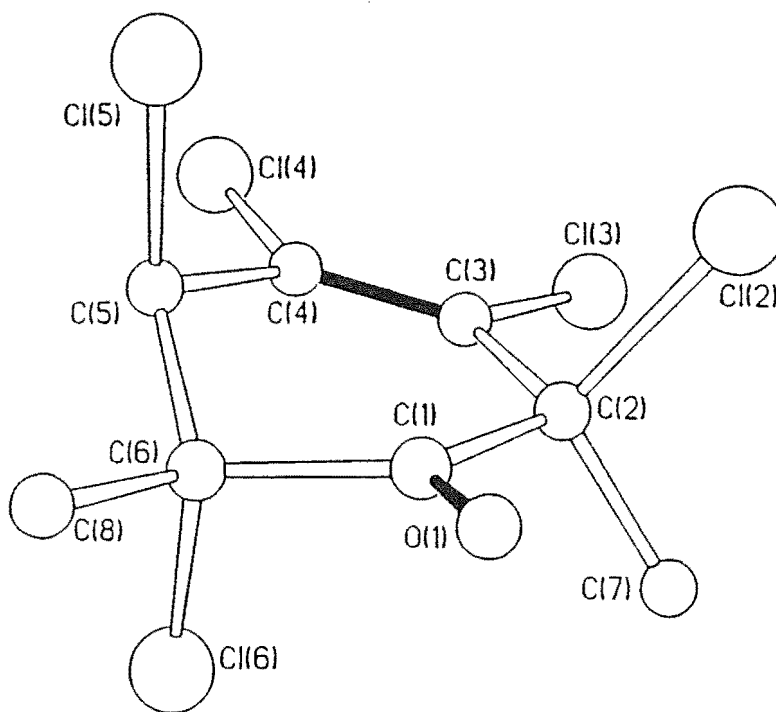
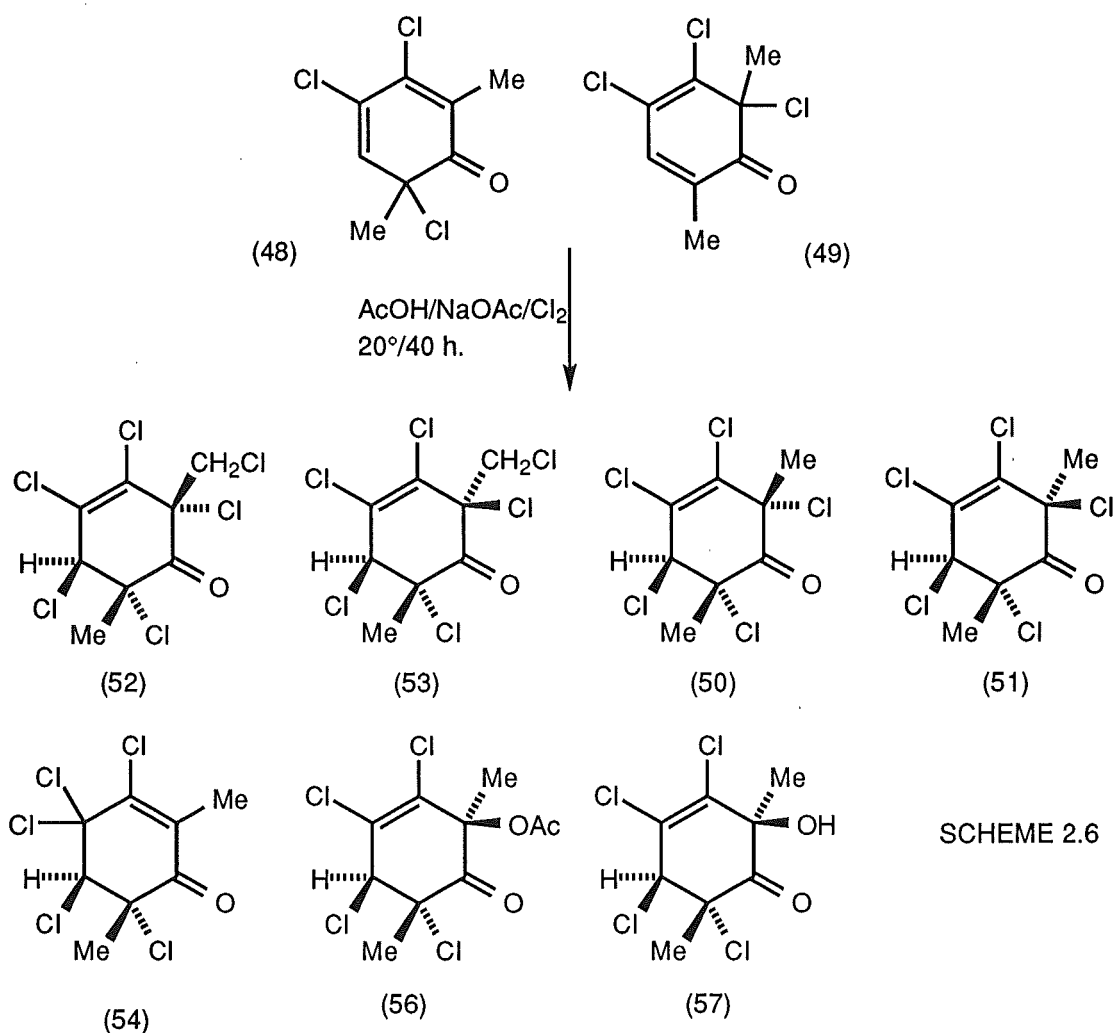


Figure 2.1 Perspective Drawing of Compound (51)

2.2.2 Reaction of Chlorine with a Mixture of 3,4,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) and 4,5,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) in Acetic Acid Containing Sodium Acetate

Reaction of a mixture of trichloro dienones (48) and (49) in acetic acid containing 1 mole equivalent of sodium acetate gave a mixture of seven compounds (Scheme 2.6, over), which were separated by chromatography.



Eluted first was *r*-2,3,4,*t*-5,*c*-6-pentachloro-2-chloromethyl-6-methylcyclohex-3-enone (52) (5%), $\text{C}_8\text{H}_6\text{Cl}_6\text{O}$, m.p. $103\text{--}105^\circ$. The structure was determined by single crystal X-ray analysis, and a perspective drawing of this compound is presented in Figure 2.2 (over) with corresponding atomic coordinates in Table 6.2. The ring exists in a flattened skew-boat conformation similar to the pentachloro ketone (51) as shown by the torsion angles $\text{C}(1)\text{--C}(2)\text{--C}(3)\text{--C}(4)$ $4.1(2)^\circ$, $\text{C}(3)\text{--C}(4)\text{--C}(5)\text{--C}(6)$ $-21.1(2)^\circ$ and $\text{C}(3)\text{--C}(4)\text{--C}(5)\text{--Cl}(5)$ $98.5(1)^\circ$. The chloromethyl function exists in a conformation with the $\text{C}(7)\text{--Cl}(7)$ and $\text{C}(2)\text{--Cl}(2)$ bonds in the *anti* orientation as shown by the torsion angle $\text{Cl}(2)\text{--C}(2)\text{--C}(7)\text{--Cl}(7)$ $179.1(6)^\circ$. The spectroscopic data for this compound is in accord with the established structure. The ^1H n.m.r. spectrum shows the chloromethyl protons appearing as an AB quartet (δ 4.009, 4.356, J 11 Hz)

because of geminal coupling. The infrared spectrum (ν_{\max} 1746, 1622) is consistent with a cyclohex-3-enone.

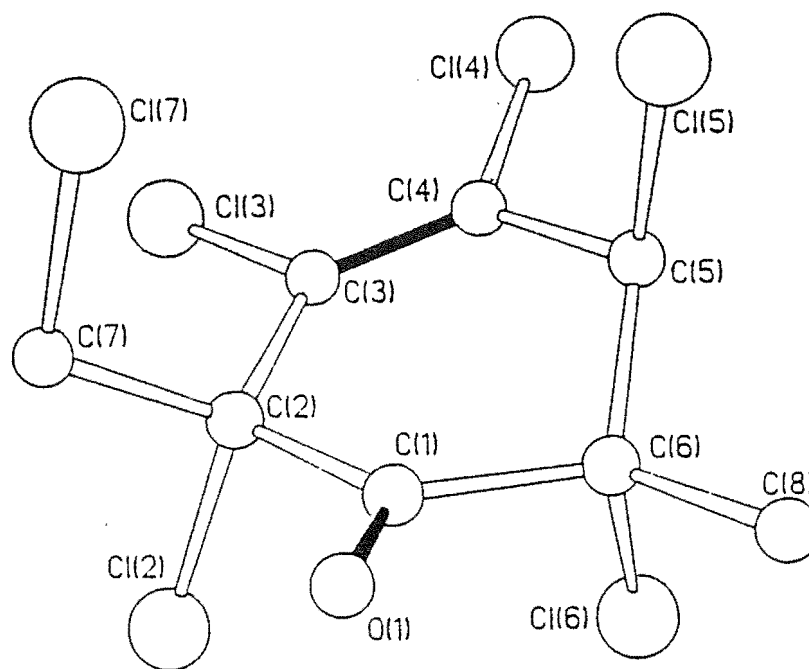


Figure 2.2 Perspective Drawing of Compound (52)

Eluted next was another chloromethyl species (53) (4%), assigned tentatively as the C2 epimer of (52) on the basis of the ^1H n.m.r. spectrum. This compound was isolated only in admixture with compound (52). The ^1H n.m.r. spectrum shows geminal coupling for the chloromethyl protons (δ 4.171, 4.302, J 11 Hz). Both the C6-methyl and H5 signals are consistent with attachment to sp^3 carbon atoms, each *ipso* to chlorine atoms. The change in the C6-methyl ^1H n.m.r. signal is not of sufficient magnitude (δ 0.072) to suggest inversion of stereochemistry at this centre, and it is also unlikely that the *trans*-5,6-dichloro arrangement should differ for this compound as the remainder of compounds from this reaction all contain this structural feature.

The next compound to be eluted was *r*-2,3,4,*t*-5,*c*-6-pentachloro-2,6-dimethyl-cyclohex-3-enone (50) (3%), identical with authentic material (Section 2.2.1).

Eluted next was the C2 epimer of the above ketone (50), namely *r*-2,3,4,*c*-5,*t*-6-pentachloro-2,6-dimethylcyclohex-3-enone (51) (28%), identical with authentic material (Section 2.2.1).

The next compound to be eluted was *trans*-3,4,4,5,6-pentachloro-2,6-dimethylcyclohex-2-enone (54) (6%), isolated only in an impure state. The structure was assigned on the basis of the spectroscopic data. The infrared spectrum (ν_{\max} 1712, 1607 cm^{-1}) indicates a conjugated enone, and the ^1H n.m.r. signal for H5 is typical of a proton attached to a sp^3 carbon, *ipso* to a chlorine. This dictates the arrangement of the double bond. The stereochemistry of the C6 substituents can be determined by comparison of the C6-methyl group ^1H n.m.r. signal with that of a similar compound (55) reported by Hartshorn *et al.*²⁹ The structure of this compound was determined by single crystal X-ray analysis, and from the perspective drawing (Figure 2.3) it can be seen that the C6-methyl group (C18) exists in an axial position.

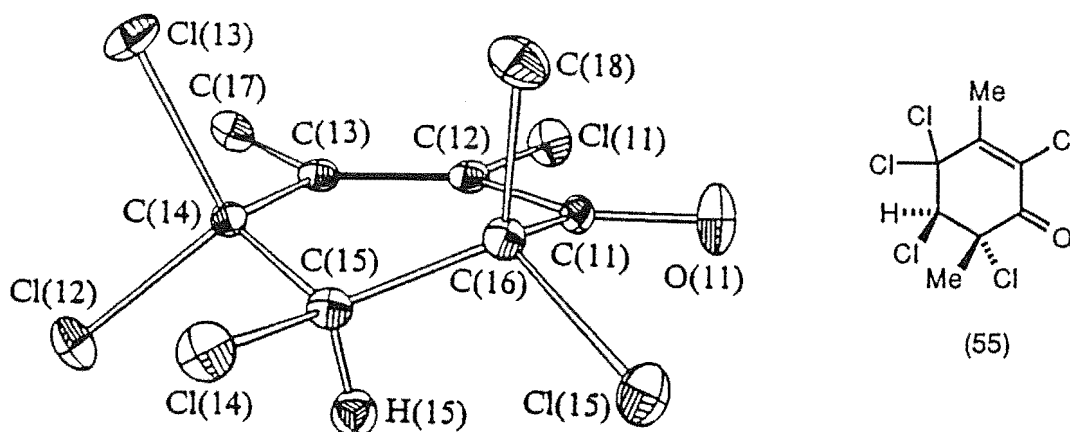


Figure 2.3 Perspective Drawing of Compound (55).

Ellipsoids are at 20 % Probability Level.

Even though the C6-methyl group is axial the deshielding affect of the C4 substituent [Cl(13)] is less than may have been expected. This is because the distance between these groups is still large. The ^1H n.m.r. spectrum of

compound (54) contains two singlets for the two methyl groups - δ 2.157 and 1.854. The downfield signal is consistent with an olefinic methyl group (i.e. C2-methyl) and the similarity of the C6-methyl signal (δ 1.854) of this compound (54) with the C6-methyl signal of compound (55) indicates a common C6 stereochemistry between these two ketones. In an analogous fashion, the similarity of the H5 signals for compounds (54) and (55) (δ 5.085 and δ 5.12 respectively) indicates the H5 proton of compound (54) is in the same orientation as H5 in compound (55), i.e. axial.

The next compound to be eluted was *r*-2-acetoxy-3,4,*c*-5,*t*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (56) (40%), $C_{10}H_{10}Cl_4O_3$, m.p. 83-86°. The structure was determined by single crystal X-ray analysis and a perspective drawing of this compound is presented in Figure 2.4, with corresponding atomic coordinates in Table 6.3.

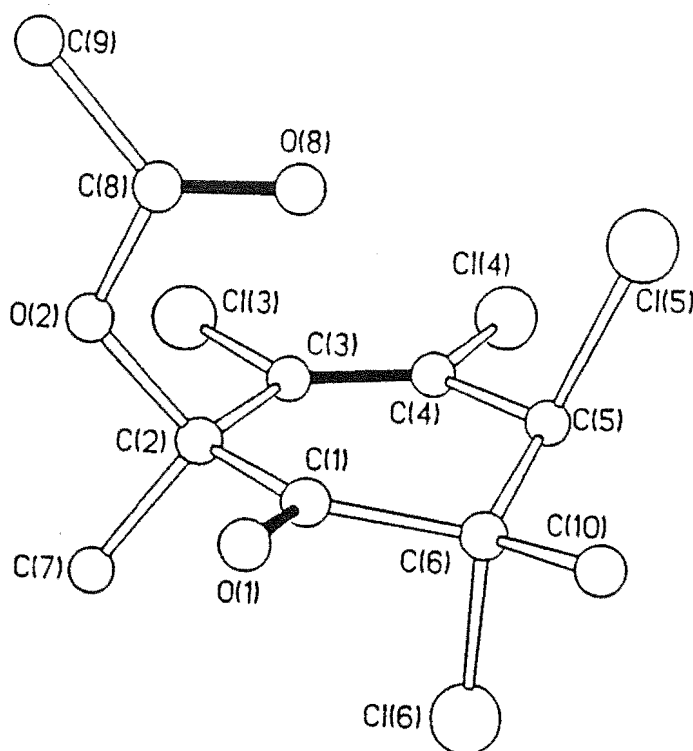


Figure 2.4 Perspective Drawing of Compound (56)

In the solid state the alicyclic ring exists in a skew-boat conformation as illustrated by the torsion angles C(1)-C(2)-C(3)-C(4) 2.1(1)°, C(3)-C(4)-C(5)-C(6)

$-20.6(2)^\circ$ and $C(3)-C(4)-C(5)-Cl(5) -105.2(1)^\circ$. The plane of the acetate function is close to co-planar with the $C(2)-C(7)$ bond [torsion angles $C(2)-O(2)-C(8)-C(9) 169.6(2)^\circ$, $C(7)-C(2)-O(2)-C(8) 167.3(1)^\circ$].

The last compound to be eluted was 3,4,*c*-5,*t*-6-tetrachloro-*r*-2-hydroxy-2,6-dimethylcyclohex-3-enone (57) (14%) $C_8H_8Cl_4O_2$, m.p. $117-120^\circ$. The structure was determined by single crystal X-ray analysis and a perspective drawing is presented in Figure 2.5, with corresponding atomic coordinates in Table 6.4. The alicyclic ring conformation is similar to the other polychlorocyclohex-3-enones formed in this reaction. Torsional angles $C(1)-C(2)-C(3)-C(4) 5.6(0.4)^\circ$, $C(3)-C(4)-C(5)-C(6) -26.8(0.4)^\circ$ and $C(3)-C(4)-C(5)-Cl(5) 94.0(0.3)^\circ$ indicate a skew-boat conformation.

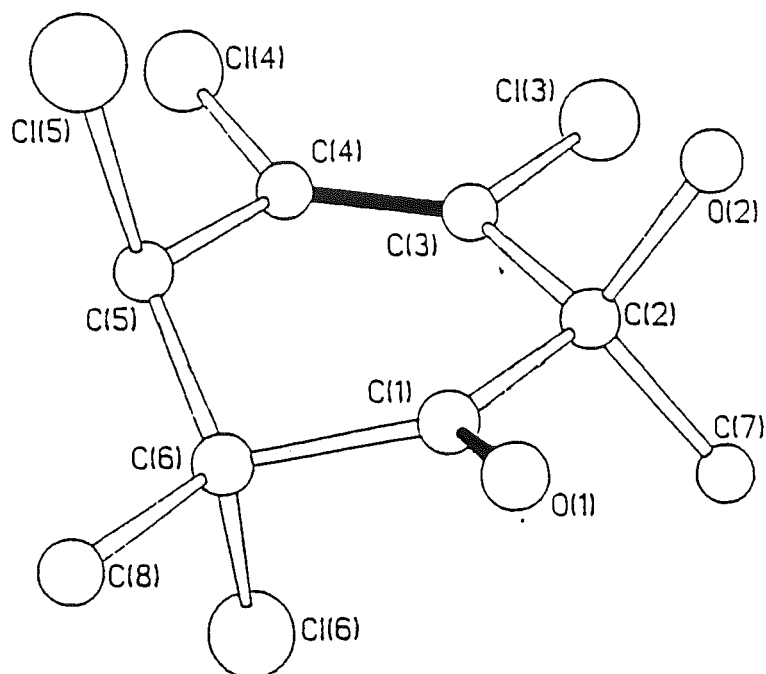


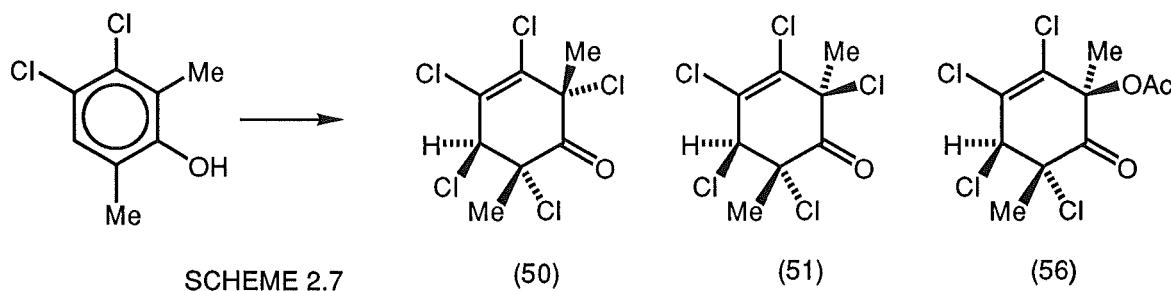
Figure 2.5 Perspective Drawing of Compound (57)

The spectroscopic data are in accord with the established structure. The 1H n.m.r. signals of the two methyl groups (δ 1.831 and 1.903) were distinguished by a n.O.e. from H5, with the C6-methyl signal showing a 0.3% increase in intensity.

The possibility that either of the pentachloro ketones (50) and (51) might rearrange in the presence of chlorine to give some or all of the remainder of the products was excluded by the observation that a mixture of these two pentachloro ketones was stable under the reaction conditions.

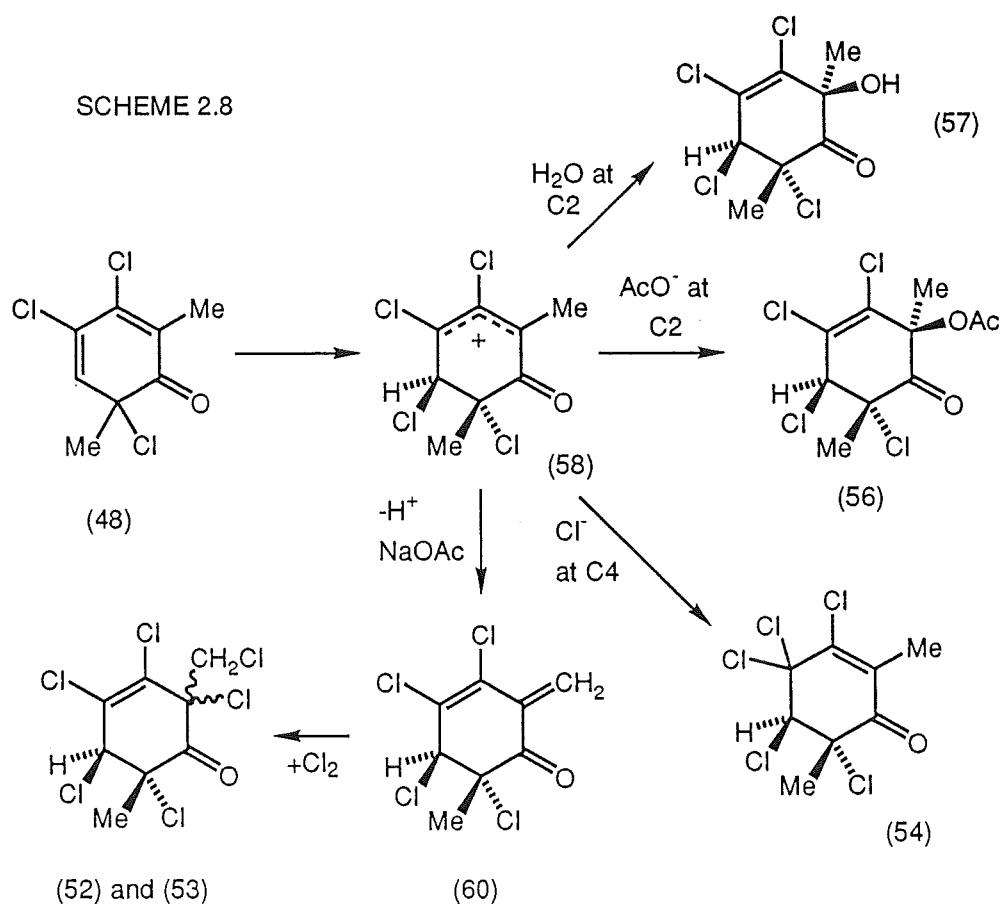
2.2.3 Reaction of Chlorine with 3,4-Dichloro-2,6-dimethylphenol in Acetic Anhydride

This reaction yielded a mixture (*ca.* 4 : 10 : 5) of three products, as shown below (Scheme 2.7). The yield of the tetrachloro acetate (56) was diminished (27%) compared with the reaction in acetic acid/sodium acetate, and the remaining two products were the two epimeric pentachloro ketones (50) and (51), with yields of 20% and 53% respectively.



2.2.4 Discussion

In the reaction of the mixture of trichloro dienones (48) and (49) with chlorine in acetic acid containing added sodium acetate the formation of compounds (52), (53), (54), (56) and (57) (total 69%) can all be accounted for in terms of initial electrophilic attack by chlorine at C5 of the 3,4,6-trichloro dienone (48) (Scheme 2.8, over).



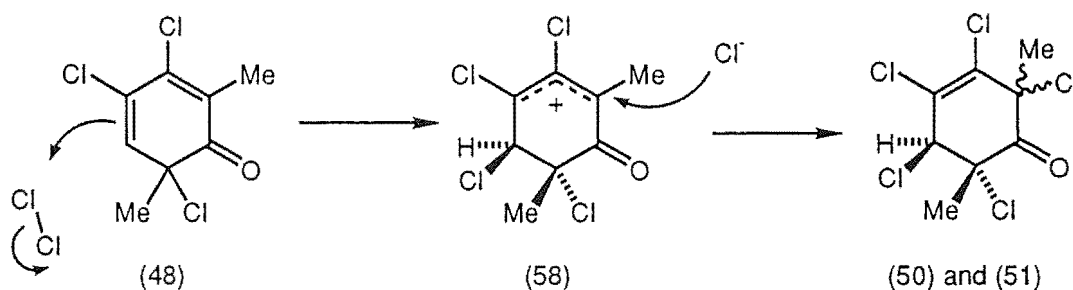
Capture of the delocalised cation (58) at C2 by either acetate ion or adventitious water accounts for the formation of the tetrachloro acetate (56) and hydroxy ketone (57) respectively, while capture by chloride ion at C4 would give the conjugated ketone (54). The formation of the chloromethyl epimers may be rationalised by abstraction of the acidic C2-methyl proton by sodium acetate to yield the methylene derivative (60). Addition of chlorine across the double bond will yield the two products (52) and (53).

If the above products are formed as depicted the total yield can only be accommodated if conversion of the 4,5,6-trichloro dienone (49) into the 3,4,6-trichloro dienone (48) occurs concurrently with the chlorine addition reaction.

In light of this observation it appears likely that the mode of formation of the two pentachloro ketones (50) and (51) (total 31%) also involves initial electrophilic attack of chlorine at C5 of the minor 3,4,6-trichloro dienone (48) to

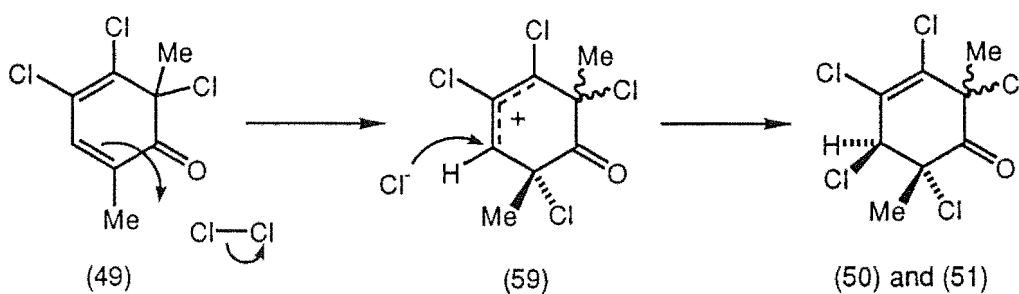
give the delocalised cation (58) which on reaction of chloride ion at C2 would give the observed products (50) and (51).

This supposition is supported by examination of the reaction paths of the two trichloro dienones (48) and (49) to form the two epimeric pentachloro ketones (50) and (51). These compounds can be viewed as being formed either by electrophilic 2,5-addition to the 3,4,6-trichloro dienone (48) (Scheme 2.9a) as postulated above, or by electrophilic 2,3-addition of chlorine to the 4,5,6-trichloro dienone (49) (Scheme 2.9b). Attack of the 3,4,6-trichloro dienone (48) at the less hindered C5 site generates the delocalised cation (58), which is captured at C2 by chloride ion to give the two products (50) and (51).



SCHEME 2.9a

Conversely, generation of a delocalised cation from the 4,5,6-dienone requires initial chlorine attack at C2, *ipso* to the methyl group. Capture of the intermediate (59) by chloride ion at C3 would give the two pentachloro ketones (50) and (51).



SCHEME 2.9b

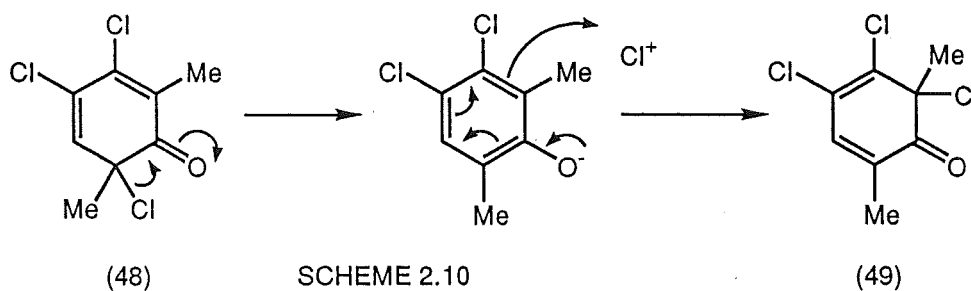
The cation formed by addition of chlorine at 3,4,6-trichloro dienone (48) should be more stable than the cation (59) formed from 4,5,6-trichloro dienone (49). The positive charge in the top structure (58) is stabilised by resonance and inductive donation of electrons from the C2-methyl group, and resonance donation of electrons from the C4-chlorine. The other structure (59) however, lacks electron donation from a methyl group, and is only stabilised by resonance donation from the C3-chlorine.

This assumption is supported by heats of formation determined using semi-empirical calculations employing the Austin Model 1 (AM1) parameter set in the MOPAC program.⁴² Heats of formation of the cations (58) and (59) were found to be 665.808 kJ mol⁻¹ and 704.665 kJ mol⁻¹ respectively.

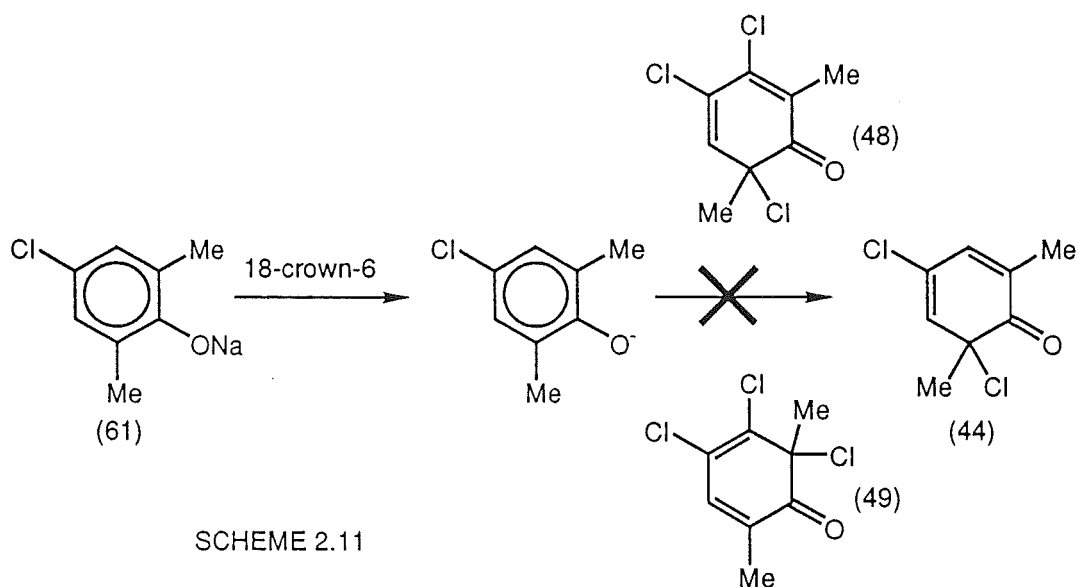
Morita and Dietrich postulated that cyclohexadienones were intermediates in the reaction of phenols with chlorine,¹⁸ and this was confirmed by Martyn.²⁵ For this reason, the lack of isolation of the dienone mixture in the reaction of 3,4-dichloro-2,6-dimethylphenol with chlorine in acetic anhydride is not believed to affect the mechanism of the reaction. The reduced yield (by 13%) of the tetrachloro acetate (56) compared with reaction in acetic acid with sodium acetate reflects the lower levels of free acetate ion in solution, in a similar manner to the reaction of 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) with chlorine in acetic anhydride (Section 2.1.3). *Cis*-2,5-addition is favoured in this solvent compared with reaction in acetic acid, presumably because of the capture of free chloride ion preventing the migration to the opposite side of the ring necessary for *trans*-2,5-addition.

2.3 Attempted Trapping of Chlorine During Dienone Interconversion:

It could be postulated that the interconversion of the two trichloro dienones (48) and (49) occurs by the formation and subsequent collapse of a phenoxide ion and Cl⁺ ion pair, as depicted over in Scheme 2.10.



If the interconversion did proceed via this pathway, the possibility existed that trapping of the Cl^+ would occur if a suitable species were present. It was decided that another phenoxide ion should act in the desired manner, with the formation of the alternative cyclohexadienone. Sodium 4-chloro-2,6-dimethylcyclohexa-2,4-dienone (61) (Scheme 2.11) was used, with sequestering of the sodium ion by complexation with a crown ether.



After two hours no 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) could be detected in the mixture by ^1H n.m.r.

2.4 Semi-Empirical Calculations of the Dienone Interconversion:

In an attempt to calculate the barriers to interconversion of the two trichloro dienones (48) and (49), *via* a [1,5]-sigmatropic shift, semi-empirical calculations were carried out on the two chloro dienones using Austin Model 1 (AM1)

parameters as implemented in the MOPAC program.⁴² Heats of formation for 3,4,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) and 4,5,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) were $-128.1 \text{ kJ mol}^{-1}$ and $-127.7 \text{ kJ mol}^{-1}$ respectively. Application of a Boltzmann distribution gave an equilibrium ratio of (48) : (49) of 54 : 46 at 22° (the experimentally observed ratio was 41 : 59.)

Further AM1 calculations were carried out to characterise the transition state in the proposed [1,5]-sigmatropic shift of chlorine. An appropriate transition state structure was determined and refined using the gradient minimisation procedure in the MOPAC program. Vibrational analysis showed a single negative eigenvalue, which indicates the structure represents a saddle point on the potential energy surface. The calculated transition state is shown below.

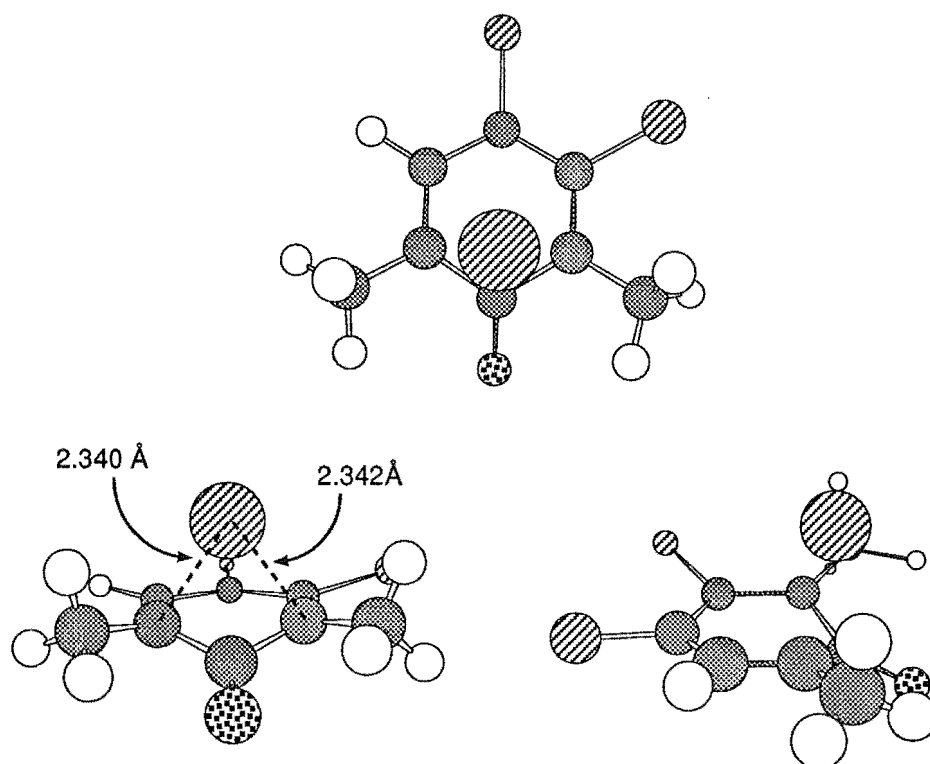


Figure 2.6 AM1 Calculated Geometry for the Transition State of the Interconversion of the Trichloro Dienones (48) and (49)

The chlorine was found to be approximately 2.34 Å from C2 and C6, and the ring structure close to planar. The carbonyl bond lies out of the plane of the ring (torsion angle C(3)-C(2)-C(1)-O(1) 145°).

A potential energy hyper-surface for the transition was calculated over 0.1 Å increments for the C2-chlorine and C6-chlorine distances. The surface is smooth with no unusual features. The saddle point and wells for the two dienones can be clearly seen (Figure 2.7).

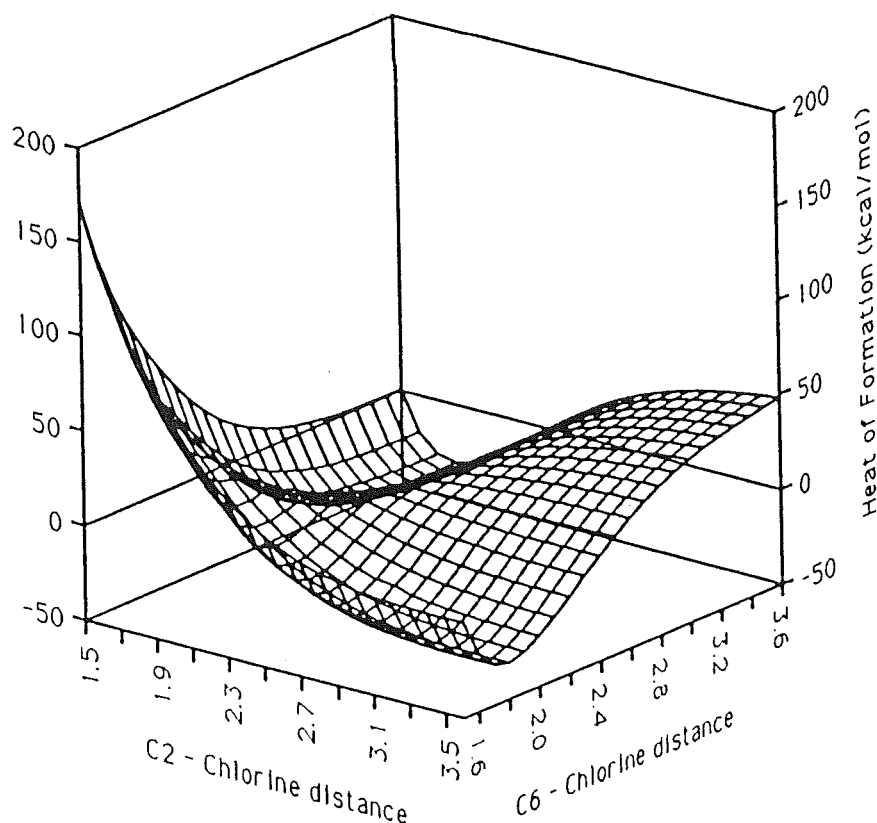


Figure 2.7 Potential Energy Hyper-surface for the Interconversion of the Trichloro Dienones (48) and (49)

The heat of formation of the transition state was calculated as 36.9 kJ mol⁻¹. This leads to a calculated barrier for the chlorine shift from the 4,5,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) to the 3,4,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) of 164.6 kJ mol⁻¹. Although this value appears to be large, previous calculations for similar [1,5]-sigmatropic shifts using analogous semi-empirical calculations tended to overestimate the barrier to transformation.⁴² It has been realised that the AM1 parameter set tends to overestimate the nuclear-nuclear repulsions at transition state distances,^{43,44} and for this reason the calculations were repeated using the later PM3 parameter set.

The PM3 calculated heats of formation for the trichloro dienones (48) and (49) were found to be $-155.7 \text{ kJ mol}^{-1}$ and $-155.8 \text{ kJ mol}^{-1}$. This corresponds to a Boltzmann distribution of 51 : 49 at 22° (observed ratio 41 : 59). The transition state was determined and minimised and the heat of formation calculated at $-16.9 \text{ kJ mol}^{-1}$. This corresponds to a barrier for the chlorine shift from the 4,5,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) to the 3,4,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) of $138.8 \text{ kJ mol}^{-1}$. Even though the PM3 paramter set is more highly optimised, the main development was seen to lie in the treatment of nitro groups, and therefore it is believed to still suffer the same faults as the AM1 method when examining transition state distances. For this reason the above value is probably again an overestimation of the barrier to interconversion.

The PM3 calculated geometry of the transition state was virtually identical to the AM1 calculated geometry. The chlorine lies almost equidistant from C2 and C6 (2.244 \AA and 2.245 \AA respectively), but slightly closer to the ring than in the AM1 model.

2.5 Discussion:

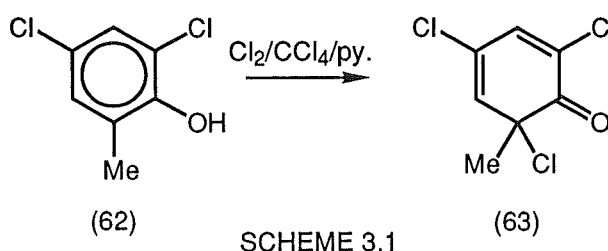
The addition of chlorine to both 2,6-dimethylphenols discussed in this chapter occur by electrophilic reaction pathways. The initial attack of chlorine occurs at an unhindered hydrogen substituted carbon to generate a delocalised cation [(47), Scheme 2.2 and (58), Schemes 2.8, 2.9] and *cis* attack of chloride ion at C2 is especially favoured in solvent systems capable of removing free chloride ion. The 4,4-dichloro moiety at C4 in the conjugated ketones (45) and (54) prevents any firm conclusions about the stereochemistry of 4,5-addition, but the observation that the yield of the 3,4,4,5,6-pentachloro compound (54) parallels the reduced yield of the *trans*-2,5-dichloro ketone (50) in sections 2.2.2 and 2.2.3 may be indicative of *trans* 4,5-addition requiring a free chloride ion migration.

It is apparent that the two trichloro dienones (48) and (49) readily interconvert by a [1,5]-sigmatropic shift of chlorine. There is a marked preference for electrophilic attack by chlorine at C5 in the 3,4,6-trichloro dienone (48) than on the 4,5,6-trichloro dienone (49).

CHAPTER THREE

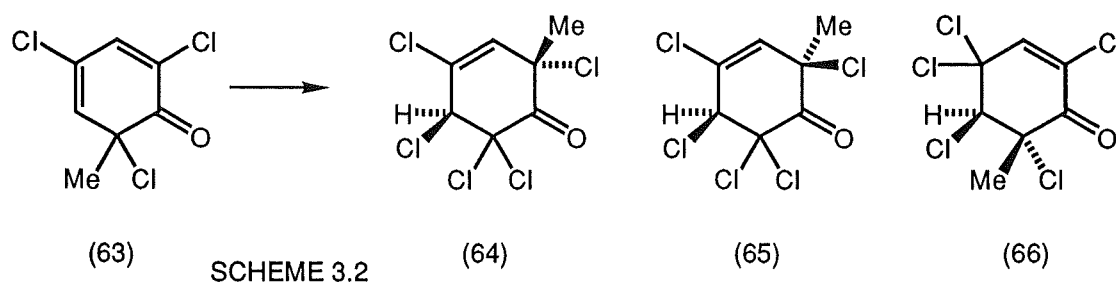
CHLORINATION OF 2,4-DIHALO-6-METHYLPHENOLS

The formation of 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (63) was carried out in the usual manner (see Section 2.1 and experimental section relating to Chapter 3). A single product was obtained, shown to be pure trichloro dienone (63), and identical with authentic material.^{25,45}



3.1 Reaction of Chlorine with 2,4,6-Trichloro-6-methylcyclohexa-2,4-dienone (63) with Chlorine in Acetic Acid:

Reaction of the trichloro dienone (63) with chlorine gave a mixture of three compounds (64), (65) and (66) (Scheme 3.2), in yields of 35%, 43% and 22% respectively, which were separated by chromatography. All three were known compounds and their structures were assigned earlier on the basis of their spectroscopic data.²⁵



The structure of the conjugated ketone (66) was confirmed by single crystal X-ray analysis. A perspective drawing of *trans*-2,4,4,5,6-pentachloro-6-methylcyclohex-2-enone, C₇H₅Cl₅O, m.p. 54-57° is presented in Figure 3.1 (two

crystallographically independent molecules in the asymmetric unit) with corresponding atomic coordinates in Table 6.5. In the solid state the two alicyclic rings exist in similar flattened half chair conformations, [torsion angles, molecule 1 C(2a)-C(3a)-C(4a)-C(5a) 15.3°, C(6a)-C(1a)-C(2a)-C(3a) 11.2°; molecule 2 C(2)-C(3)-C(4)-C(5) 18.0°, C(6)-C(1)-C(2)-C(3) 1.6°]. In both molecules the C5-chlorine exists in the equatorial position as shown by the torsion angles Cl(7)-C(5a)-C(6a)-C(1a) 179.7° and Cl(3)-C(5)-C(6)-C(1) 178.4°, as is usual for cyclohex-2-enes.²⁹

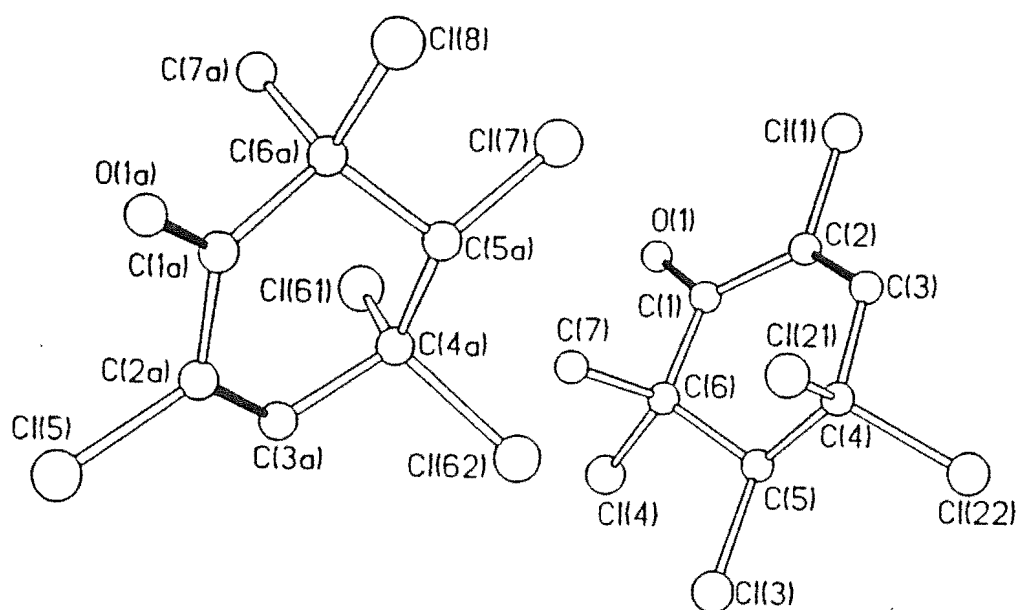
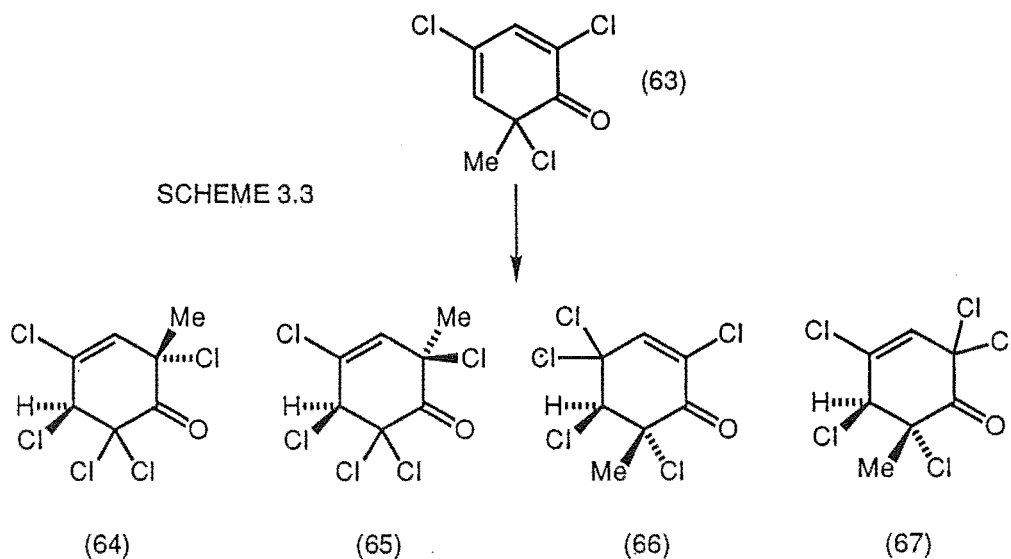


Figure 3.1 Perspective Drawing of Compound (66)

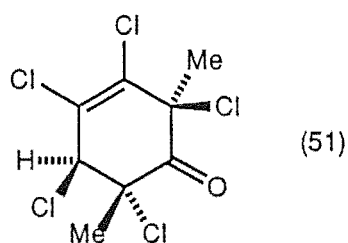
3.2 Reaction of Chlorine with 2,4,6-Trichloro-6-methylcyclohexa-2,4-dienone (63) in Acetic Acid Containing Sodium Acetate:

A 24 hour reaction of the trichloro dienone (63) with chlorine in acetic acid/sodium acetate gave the above three pentachloro ketones and one new compound (67) (Scheme 3.3, over). The components of the mixture were separated by chromatography.



The yields of the two C2-epimeric ketones (64) and (65) were both greatly reduced (to 9% each), although the yield of the cyclohex-2-enone (66) was increased slightly (27%). The remainder of the mixture comprised the ketone (67), at 55%. The structure of this compound was assigned on the basis of the spectroscopic data.

The infrared spectrum (ν_{\max} 1759, 1645) for compound (67) indicates a non-conjugated enone system, and the C5/C6 stereochemistry was assigned after comparison with compound (51).

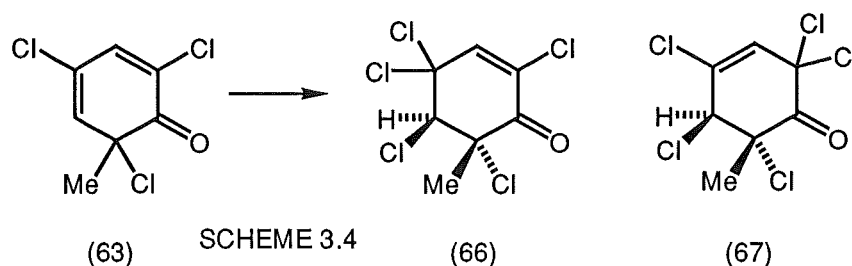


The X-ray structure of compound (51) showed the C6-methyl group (C8) exists in the equatorial position, and the lack of deshielding by diaxial interactions with chloro substituents accounts for the upfield position of its ^1H n.m.r. signal (δ 1.941). In comparison, the methyl ^1H n.m.r. signal of compound (67) is similar (δ 1.947), indicating a common arrangement at C6. Given the established conformational characteristics of such 5,6-dichlorocyclohex-3-enones, which includes the presence of the 5-Cl function in either the flagpole

orientation on a flattened skew boat conformation or *pseudo*-axial on a flattened half chair conformation,²⁹ the 5,6-dichloro stereochemistry of compound (67) must be *trans*.

3.3 Reaction of Chlorine with 2,4,6-Trichloro-6-methylcyclohexa-2,4-dienone (63) in Acetic Anhydride:

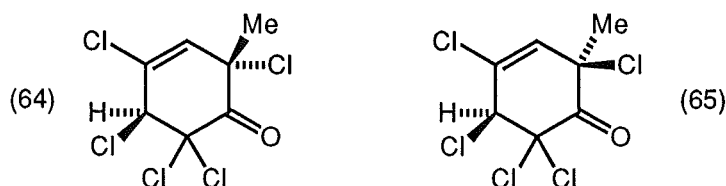
Reaction of the trichloro dienone (63) with chlorine in acetic anhydride gave only two products as shown in Scheme 3.4.



The yield of the non-conjugated ketone (67) was greatly increased (84%), and the cyclohex-2-enone (66) comprised the remainder of the mixture (16%).

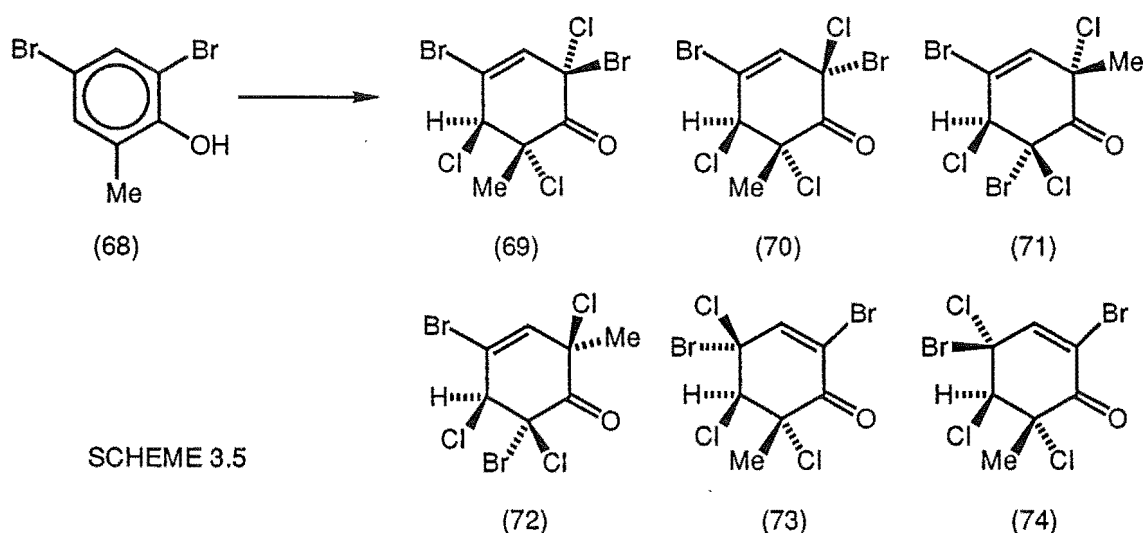
3.4 Reaction of Chlorine with 2,4-Dibromo-6-methylphenol (68) in Acetic Acid:

The *gem*-6,6-dichloro moiety of the *trans*- and *cis*-pentachloro ketones (64) and (65), and the *gem*-4,4-dichloro and *gem*-2,2-dichloro moieties in compounds (66) and (67) respectively means a great deal of information concerning the stereochemistry of the chlorine addition is obscured.



For this reason, the chlorination reactions of the corresponding bromo phenol (68) were examined. The similarities in behaviour of bromine and chlorine as substituents on the phenolic ring were demonstrated by R. J. Martyn,²⁵ who

showed the reaction of 2,4-dibromo-5,6-dimethylphenol (109) (Section 5.2) with chlorine behaved exactly as had the corresponding dichloro phenol. One difference noted by Martyn was the instability of bromochloro dienones. For this reason, and the observation that phenols react to give essentially the same products as the corresponding cyclohexa-2,4-dienones (see Section 2.2.4), the phenol (68) was chlorinated directly (Scheme 3.5), and no attempt was made to isolate the dibromochloro dienone. As shown below, six products were formed in the reaction, which were separated by chromatography.



Eluted first was *r*-2,4-dibromo-2,*c*-5,*t*-6-trichloro-6-methylcyclohex-3-enone (69) (30%), and the structure was assigned on the basis of its spectroscopic data. The infrared spectrum (ν_{\max} 1757, 1638) indicates a non-conjugated enone structure. This is supported by allylic coupling in the ^1H n.m.r. spectrum, from H3 to H5 (J 1.5 Hz). The rest of the structure was assigned after comparison with another compound (70), its C2 epimer (see below). The structure of compound (70) was determined by single crystal X-ray analysis, and showed that the chlorine addition had occurred to C2/C5, and that the methyl group was attached to C6. The orientation of the latter was equatorial, as suggested by its upfield ^1H n.m.r. signal (δ 1.928). Compound (69) displayed a very similar ^1H n.m.r. spectrum. The upfield signal of the methyl group (δ 1.950) indicates this group also exists in the equatorial position. If the stereochemistry

at this centre were inverted, with the methyl group in the axial orientation, it would experience a 1,3-diaxial interaction with the C2 axial halo-substituent and the methyl ^1H n.m.r. signal would appear c. 0.1-0.3 ppm downfield from the observed position. As mentioned for compound (67) (above), the 5,6-dichloro stereochemistry will be *trans*.

The second compound to be eluted was the dibromo-trichloro ketone (70) (15%), $\text{C}_7\text{H}_5\text{Br}_2\text{Cl}_3\text{O}$, m.p. $53\text{--}55^\circ$, and the structure was determined by single crystal X-ray analysis. A perspective drawing of this compound is given below, Figure 3.2, with corresponding atomic coordinates in Table 6.6.

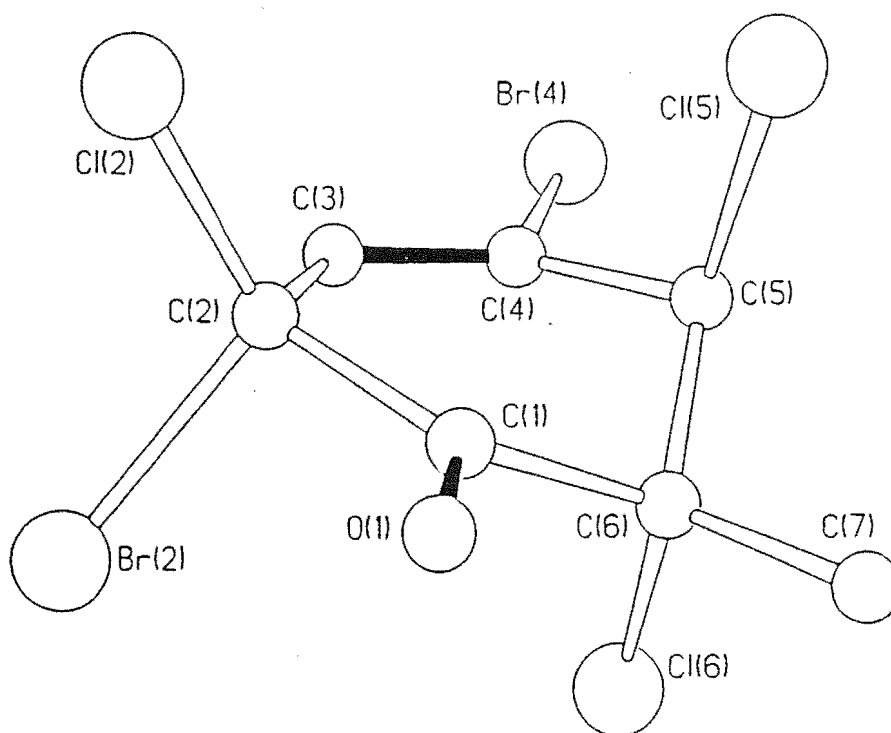
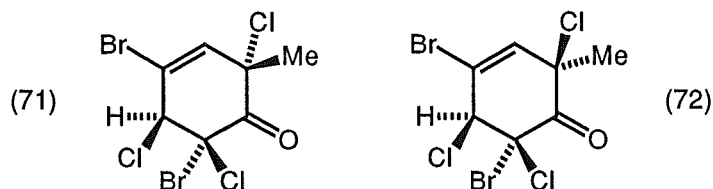


Figure 3.2 Perspective Drawing of Compound (70)

The crystal was of poor quality and, although a clear solution emerged, the data was not of sufficient quality to allow refinement below a R value of 8.6%. In the solid state the alicyclic ring exists in a skew-boat conformation [torsion angles $\text{C}(1)\text{--C}(2)\text{--C}(3)\text{--C}(4)$ -17.1° , $\text{C}(3)\text{--C}(4)\text{--C}(5)\text{--C}(6)$ 40.0° and $\text{C}(3)\text{--C}(4)\text{--C}(5)\text{--Cl}(5)$ -70.7°]. The spectroscopic data are in accord with the established structure.



The third compound eluted was the ketone (71), which could only be isolated as a minor component in admixture with compounds (70) and (72), even though it was a major species (30%) in the initial product mixture. The structure was assigned on the basis of its ^1H n.m.r. spectrum. The position for the signal of the olefinic proton H3 (δ 6.391) is indicative of a non-conjugated enone; a conjugated enone system would display this signal 1.0-1.5 ppm further downfield. The H5 signal (δ 5.107) is typical for a proton in the equatorial position attached to a carbon atom *ipso* to a chlorine atom adjacent to a carbon bearing two halogen substituents. The signal from the methyl group occurs upfield (δ 1.867) indicating a lack of deshielding. This suggests the methyl group is in the equatorial orientation, and *cis* to the C5-chlorine atom. The stereochemistry at C6 was assigned on the basis of mechanistic details and is discussed further in Section 3.7.

The fourth compound to be eluted was the 4,6-dibromo-2-methyl ketone (72) (15%), $\text{C}_7\text{H}_5\text{Br}_2\text{Cl}_3\text{O}$, m.p. 58-62°, and the structure was determined by single crystal X-ray analysis. A perspective drawing of compound (72) is presented in Figure 3.3 (over) with corresponding atomic coordinates in Table 6.7. The alicyclic ring exists in a flattened skew-boat conformation as shown by the torsion angles C(1)-C(2)-C(3)-C(4) 9.2°, C(3)-C(4)-C(5)-C(6) -31.2° and C(3)-C(4)-C(5)-Cl(5) 90.8°. The spectroscopic data are in accord with the established structure. The ^1H n.m.r. signal of the methyl group is shifted downfield (to δ 2.110) by deshielding from the C6-bromine, and the H3 and H5 signals exhibit allylic coupling (J 1.5Hz).

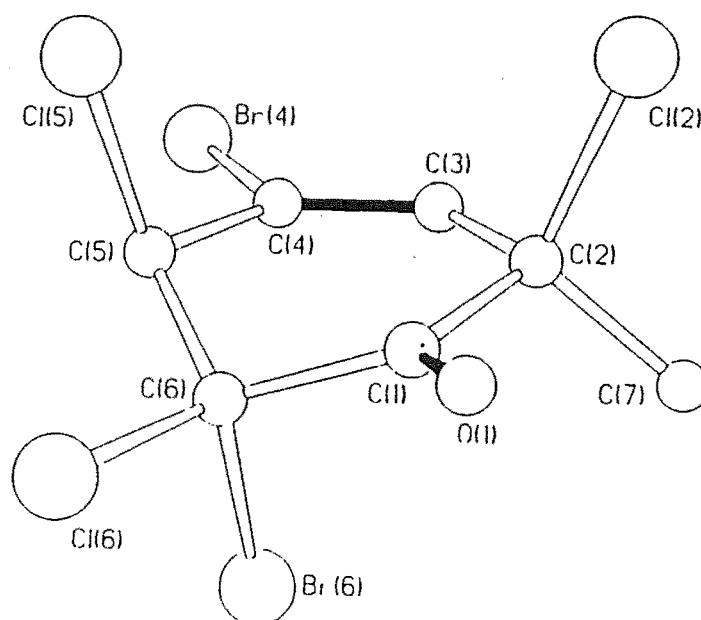
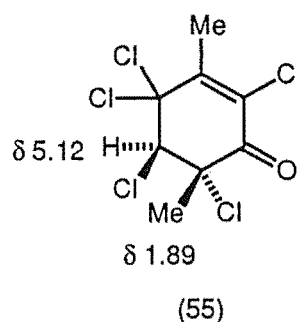
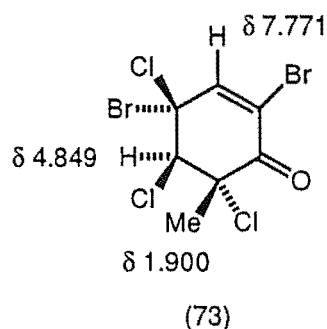


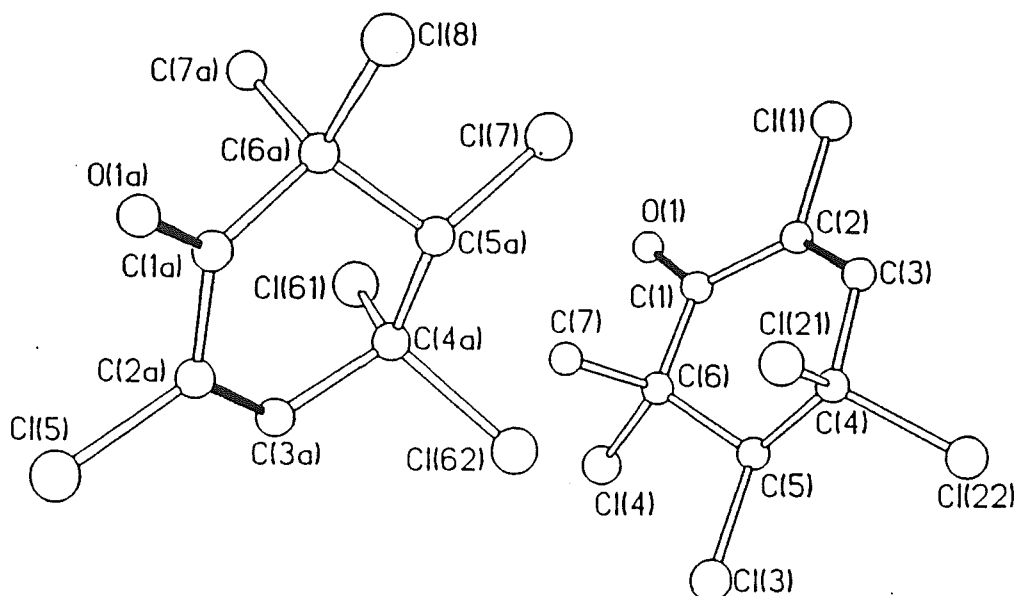
Figure 3.3 Perspective Drawing of Compound (72)

The next compound to be eluted was the conjugated enone (73) (5%), and its structure was assigned on the basis of its spectroscopic data. The infrared spectra (ν_{\max} 1718, 1599), the downfield position of the olefinic proton (δ 7.771) and the upfield position of the methyl group (δ 1.900) in the ^1H n.m.r. indicate the position of the double bond. The conjugation pattern is supported by the ultraviolet spectrum (λ_{\max} 279 nm, ϵ 1820). The arrangement of substituents at C5 and C6 was assigned after comparison with compound (55).



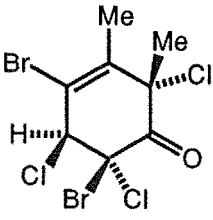
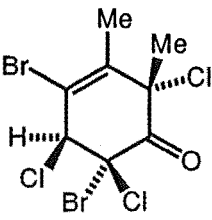
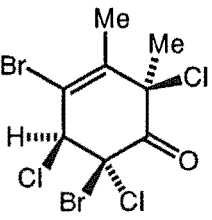
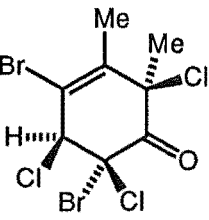
The similarity of the C6-methyl signals of these compounds (δ 1.89 and 1.900) is supportive of a *trans*-5,6-dichloro arrangement. As in compound (69) the ^1H n.m.r. signal of H3 reflects the arrangement of the C4 substituents. These two groups on C4 of cyclohex-2-enones adopt *pseudo*-axial and *pseudo*-equatorial

positions with respect to H3. This is illustrated in the torsion angles of compound (66) H(3)-C(3)-C(4)-Cl(21) 70.7°, H(3)-C(3)-C(4)-Cl(22) -44.1°, H(3a)-C(3a)-C(4a)-Cl(61) 68.7° and H(3a)-C(3a)-C(4a)-Cl(62) -45.8°.

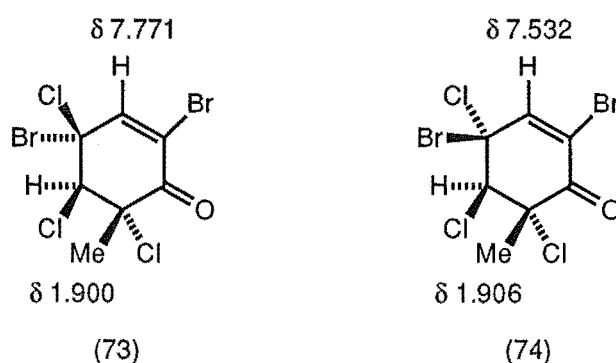


Perspective Drawing of Compound (66)

R. J. Martyn showed through a X-ray structure of the dibromo trichloro ketone (77) (over) that H5 exists in a *gauche* arrangement with the two C6 substituents, although closer to the axial substituent [Br(6)-C(6)-C(5)-H(5) -64.4°; Cl(6)-C(6)-C(5)-H(5) 55.0°]. Hence, the C6-axial substituent should have a larger effect on the shielding or deshielding experienced by H5. It was demonstrated for the C2 and C6 epimers of (77), namely (75), (76) and (78) (over) that a bromo substituent in the axial position at C6 will deshield H5 to a greater extent than a chlorine in the axial position (e.g. compound (76) δ 5.18 vs. compound (75) δ 5.14, and compound (78) δ 5.23 vs. compound (77) δ 5.18). The observation was also made that a bromine in the C6 axial position deshielded the axial C2-methyl group to a greater extent than did a C6 axial chlorine (e.g. compound (78) δ 2.13 vs. compound (77) δ 2.05).

			
(75)	(76)	(77)	(78)
¹ H n.m.r.			
H5	5.14	5.18	5.23
2-Me	1.88	1.88	2.13

If it is accepted that bromine has a greater deshielding effect than chlorine then the stereochemistry at C4 of compound (73) can be assigned on the basis of the ¹H n.m.r. signal of H3. When a C4-bromine is in the *pseudo*-equatorial position it should deshield H3 to a greater extent than when the C4-chlorine is in the *pseudo*-equatorial position. Similarly, a *pseudo*-axial bromine should deshield the C6-methyl group to a greater extent than a *pseudo*-axial chlorine. After comparison with the ¹H n.m.r. spectrum of the C4 epimer, compound (74) (below) it appears that in compound (73) the C4 bromine exists in the *pseudo*-equatorial position, *trans* to the C5-chlorine.

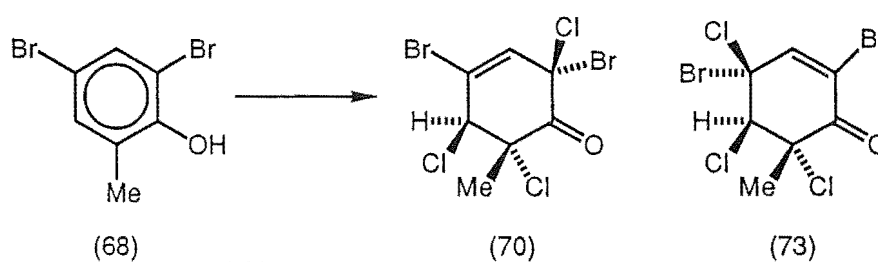


The last compound to be eluted is the C4 epimer of the above compound (73), namely the conjugated ketone (74) (5%). This compound could not be isolated in a pure state, and the structure was assigned on the basis of the ¹H n.m.r. spectrum, after comparison with the ¹H n.m.r. spectrum of compound (73). The downfield position of the olefinic proton (δ 7.532) is indicative of the conjugation pattern, and the similarities of the H5 and methyl signals (δ 4.857,

1.906) with those of compound (73) (δ 4.849, 1.900) support a common orientation for these groups. By exclusion the chlorine at C4 exists in the *pseudo*-equatorial position, *trans* to the C5-chlorine atom.

3.5 Reaction of Chlorine with 2,4-Dibromo-6-methylphenol (68) in Acetic Anhydride:

Reaction of the phenol (68) with chlorine in acetic anhydride gave only two products, as shown in Scheme 3.6.



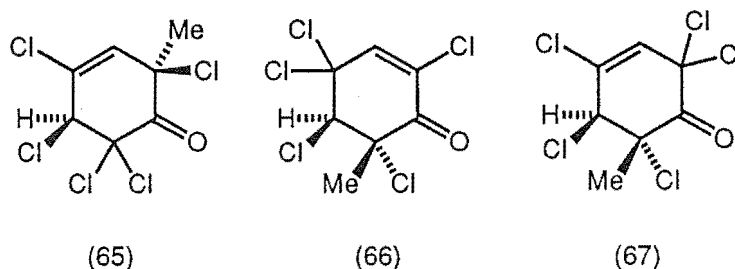
Both of these compounds had been observed in the reaction in acetic acid (Section 3.4) and were separated by chromatography. The yield of the cyclohex-3-enone (70) was 77%, compared with 15% in the acetic acid reaction. The conjugated ketone (73) comprised the remainder of the mixture (23%).

3.6 Solvent Effect Study:

Due to the large variations in yields of the products on changing solvent, a study was undertaken to explore this effect further. The trichloro dienone (63) was reacted with excess chlorine in mixtures of acetic acid and acetic anhydride, ranging from 90% Ac_2O : 10% AcOH to 1% Ac_2O : 99% AcOH (see experimental section relating to Chapter Three).

At high levels of acetic anhydride the reaction gave a similar product ratio to the reaction in pure acetic anhydride (Section 3.3), but with a small amount of

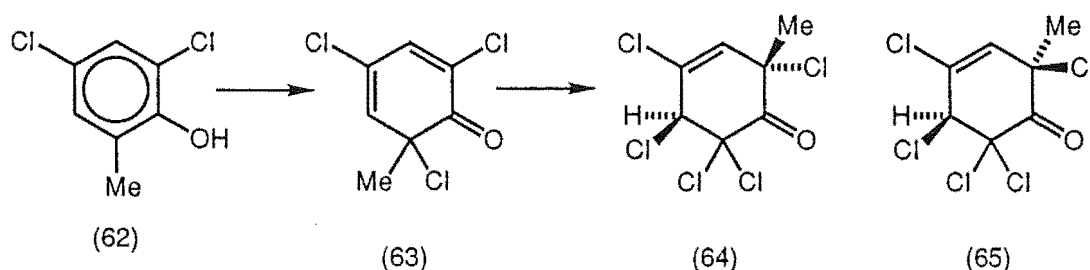
the *cis*-2,5-dichloro ketone (65). Only at very low levels of acetic anhydride did the yield of this compound (65) increase, and the yield of the conjugated ketone (66) decrease. The yield of the 2,2,4,5,6-pentachloro ketone (67) dropped slowly over the whole range.



3.7 Discussion:

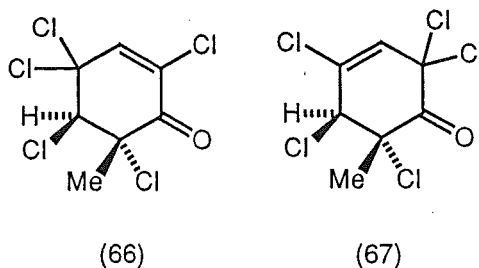
The change in product mixtures on changing solvent systems indicates that chlorine addition to the dichloro phenol (62) in acetic acid occurs by nucleophilic mechanisms. This can be inhibited by the addition of sodium acetate or by changing the solvent to acetic anhydride, thus removing from the system the free chloride ion needed for the nucleophilic chlorine addition and forcing instead electrophilic chlorine addition.

The two compounds (64) and (65) form by nucleophilic 2,3-addition to the trichloro dienone (63). From the reaction in acetic acid/sodium acetate and the reaction in acetic anhydride it can be seen that the pentachloro ketone (67) is formed by electrophilic 2,5-addition.



The origin of the conjugated ketone (66) in the reactions in acetic acid and in acetic acid/sodium acetate is less clear. The reasonable yield of this compound

in the reaction in acetic anhydride (23%) indicates that this compound can form by electrophilic 4,5-addition to the trichloro dienone (63).



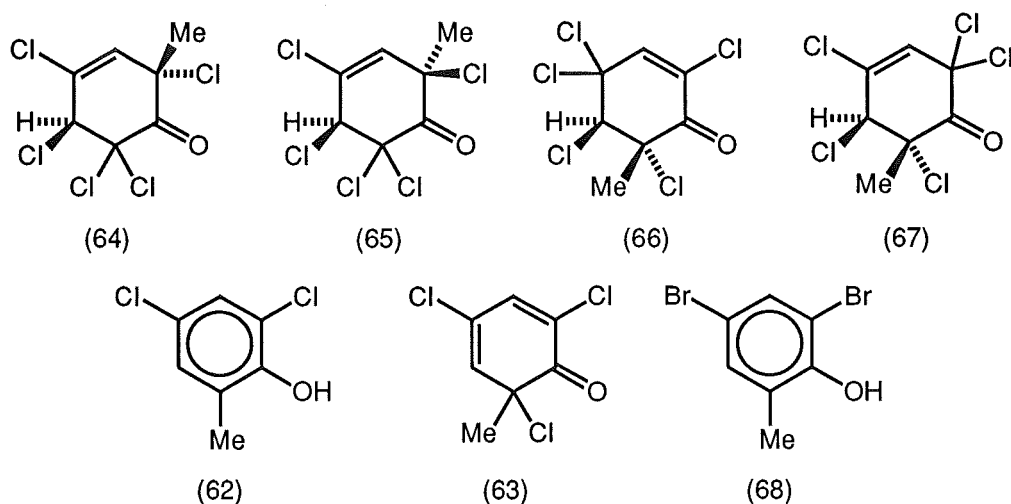
In the reaction in acetic acid, the cyclohex-2-enone (66) may form by either electrophilic or nucleophilic 4,5-addition. The parallel formation of the two nucleophilic 2,3-addition products (64) and (65) however tends to favour the nucleophilic mechanism for the formation of compound (66). As the ketone (67) forms by electrophilic addition, and this compound is not observed in the reaction mixture it is unlikely that the conjugated ketone (66) forms by electrophilic addition. In the reaction in acetic acid/sodium acetate compound (66) presumably forms mostly by electrophilic addition, but there may be some residual nucleophilic addition. No nucleophilic 2,5-addition was observed in this case.

The addition of sodium acetate to acetic acid inhibits most nucleophilic addition and the electrophilic addition products compounds (66) and (67) form preferentially. However in this solvent there is some residual nucleophilic addition occurring (compounds (64) and (65) - total yield 18%).

The results of the solvent effect study may be accounted for on the reasonable assumption that the nucleophilic addition of chlorine requires free chloride ion. As demonstrated by Satchell,²⁶ acetic anhydride can act as an effective trap for free chloride ion. At very low acetic anhydride levels trapping of chloride ion is incomplete, and the more favoured nucleophilic addition becomes

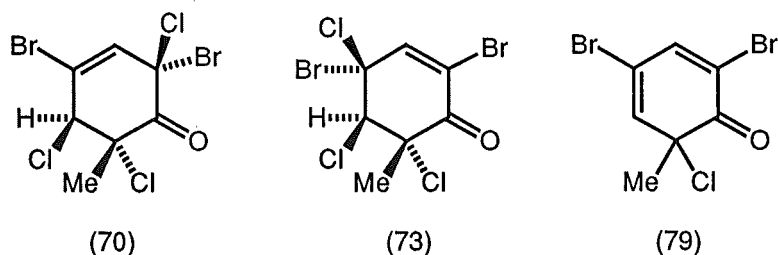
predominant. It is worth noting however, that at acetic anhydride levels as low as 1%, some suppression of nucleophilic addition is still occurring.

As mentioned in Section 3.4 the *gem*-dichloro arrangement in the four products (64), (65), (66) and (67) restricts the acquisition of information about the stereochemistry of the chlorine addition. The products from the chlorination of the dibromo phenol (68) can be used as a basis for comparison for the mode of formation of the products of the reactions of the dichloro phenol (62) with chlorine.



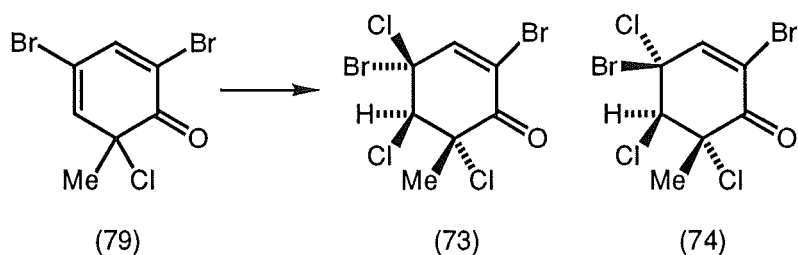
The reaction of the dibromo phenol (68) with chlorine in acetic anhydride gave two products (70) and (73) which correspond to the products (67) and (66) formed in the chlorination of the trichloro dienone (63) in acetic anhydride (Schemes 3.4 and 3.6). Martyn showed that the chlorination of a phenol proceeds through a cyclohexadienone,²⁵ and for the dibromo phenol (68) it is believed that the reaction gives initially 2,4-dibromo-6-chloro-6-methylcyclohexa-2,4-dienone (79) (over), which is further chlorinated. If this is accepted then it can be said that the formation of the 2,4-dibromo-6-methyl ketone (70) occurs stereoselectively by *cis* addition of chlorine across C2/C5. There is no evidence to indicate that the dibromo phenol (68) reacts in a different manner from the dichloro phenol in this reaction, so it is believed that compound (67) is formed by stereoselective *cis* 2,5-addition of chlorine to the trichloro dienone

(63). As in Section 2.2.4 *trans* addition will require migration of free chloride ion to the opposite face of the ring, and this will be prevented by reaction with the solvent.



It follows that the formation of the dibromo conjugated ketone (73) occurs by chlorine addition to C4/C5 of the dibromochloro dienone (79). The stereochemistry at C4 of this compound indicates that this addition occurs stereoselectively in a *cis* manner. It is believed that suppression of *trans* addition by reaction of acetic anhydride with free chloride ion is responsible for lack of the C4 epimer (74). In both compounds (70) and (73), the arrangement of chloro substituents at C5/C6 is *trans*.

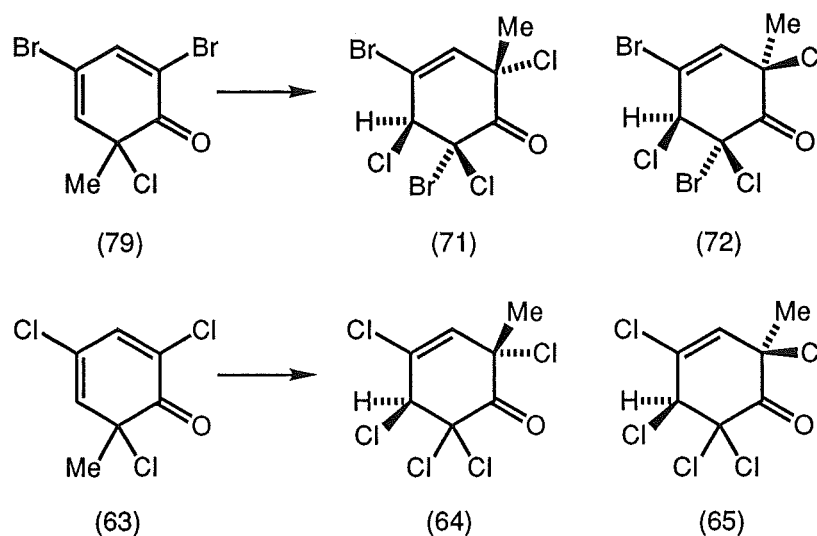
The reaction of the bromo phenol (68) with chlorine in acetic acid gave three pairs of epimers. As in the acetic anhydride reaction, chlorination will proceed through the cyclohexadienone (79). The isolation of the two conjugated ketones (73) and (74), epimeric at C4, indicates that 4,5-addition, in this case occurs both *cis* and *trans* to C4/C5, yet the chlorine arrangement across C5/C6 is still exclusively *trans*.



As there is no species present to trap free chloride ion this addition may occur by electrophilic and/or nucleophilic mechanisms. As mentioned above, the electrophilic reaction gave only the *cis* isomer (73), but this selectivity is

presumed to be caused merely by the solvent preventing *trans* addition by reaction with free chloride ion.

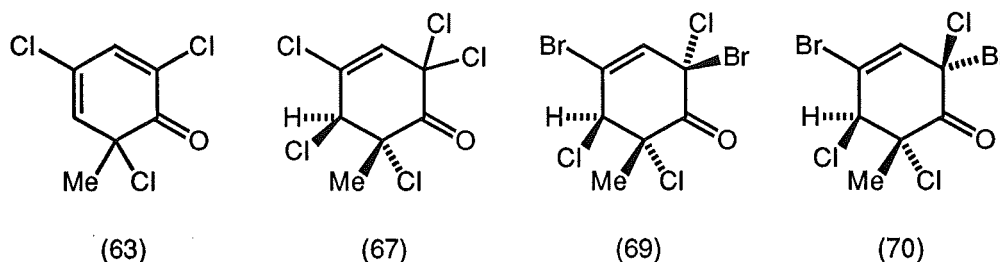
The two 4,6-dibromo-2-methyl ketones (71) and (72) correspond to the *cis* and *trans* ketones (64) and (65) formed in the reaction of chlorine with the trichloro dienone (63) in acetic acid.



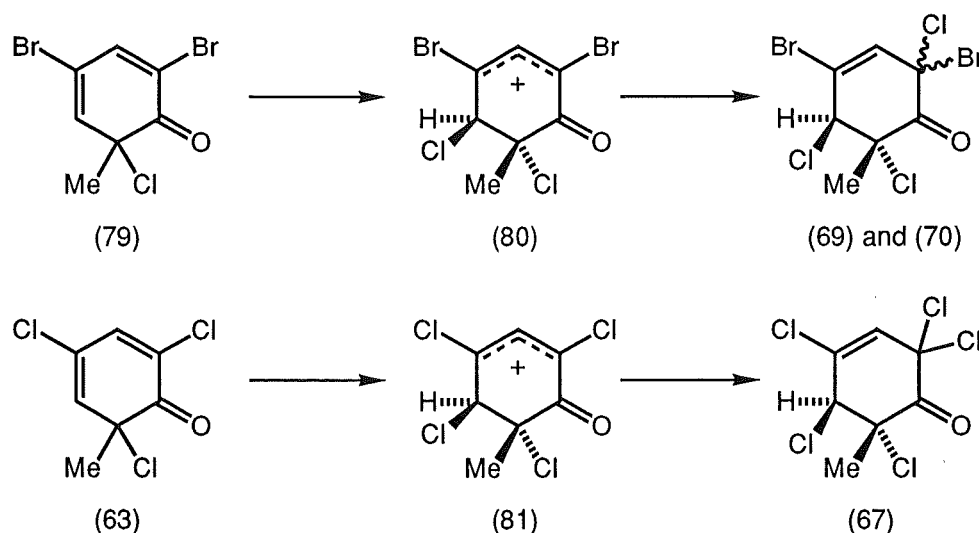
As the pentachloro ketones (64) and (65) form by nucleophilic addition, the origin of (71) and (72) is believed to be the same i.e. nucleophilic 2,3-addition. This is supported by the absence of compounds (71) and (72) among the products of the acetic anhydride reaction (Section 3.5). The observation that the C6-epimer of compound (72) is not formed implies that nucleophilic 2,3-addition occurs to the dibromochloro dienone (79) exclusively *cis* to give the observed C5/C6 arrangement in compounds (71) and (72). Both C2-epimers are produced in this reaction, but addition of the first chlorine to the cyclohexadienone (79) occurs preferentially *cis* to the C2-methyl group. Addition in this fashion yields compound (71) (30%), which is favoured over the product arising from initial attack *trans* to the methyl group (72) (15%).

The final pair of epimers in the bromo phenol reaction in acetic acid are the compounds (69) and (70) (over). These correspond to the compound (67) in the

chloro phenol case, which is known to arise from electrophilic 2,5-addition.



It is known that the trichloro dienone (63) does not react by electrophilic mechanisms in acetic acid as the pentachloro ketone (67) is not observed in this reaction (Section 3.1). However, it is possible that the bromo dienone (79) may react by electrophilic pathways in acetic acid to give compounds (69) and (70). The difference arises because compared with chlorine, bromine has a lower electronegativity (Cl 2.83, Br 2.74),⁴⁶ making bromine a weaker inductive electron acceptor. This dissimilarity becomes apparent in the stabilisation of the delocalised cation intermediate in the electrophilic reaction pathway (Scheme 3.7).

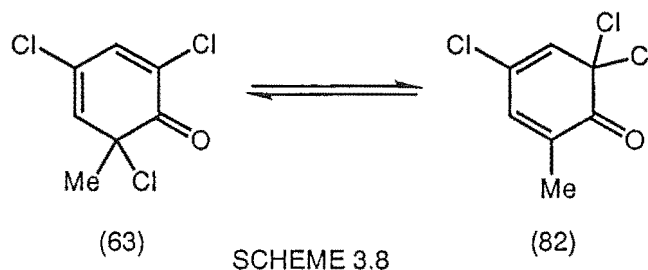


SCHEME 3.7

The cation (80) will be more stable than (81) as bromine can better stabilise the positive charge. This is believed to be enough to allow electrophilic addition to occur to the bromo dienone (79). However the possibility that compounds (69) and (70) are formed by nucleophilic addition cannot be excluded.

3.8 Semi-Empirical Calculations of a Possible Dienone Interconversion:

The trichloro dienone (63) was studied by semi-empirical calculations to see if a [1,5]-sigmatropic shift might be occurring to give the dienone (82) (Scheme 3.8).



The AM1 parameter set was used to calculate the heats of formation for both of these dienones, using the MOPAC program. These were found to be $-98.0 \text{ kJ mol}^{-1}$ and $-96.8 \text{ kJ mol}^{-1}$ for (63) and (82) respectively. Application of a Boltzmann distribution gives a ratio for (63) : (82) of 88 : 12 at 22° . (The experimentally observed value was 100 : 0). The heat of formation for the transition state was calculated at 63.2 kJ mol^{-1} , which corresponds to a barrier to interconversion of $166.3 \text{ kJ mol}^{-1}$ for interconverting (63) to (82). Although this value is of similar magnitude to that of the interconversion of the two trichloro dimethyl dienones (48) and (49) (Section 2.4), which are known to interconvert, and a Boltzmann ratio of 88 : 12 for (63) : (82) is predicted, the 4,6,6-trichloro dienone (82) is not observed experimentally. (See Appendix Two).

As a comparison the above calculations were repeated with the PM3 parameter set. The heats of formation of (63) and (82) were calculated as being $-121.8 \text{ kJ mol}^{-1}$ and $-123.4 \text{ kJ mol}^{-1}$ respectively. This corresponds to a Boltzmann distribution for (63) : (82) of 7 : 93 at 22° (experimental value = 100 : 0). The heat of formation of the transition state was found to be 17.3 kJ mol^{-1} , giving a barrier to interconversion of $139.1 \text{ kJ mol}^{-1}$ for (63) interconverting to (82).

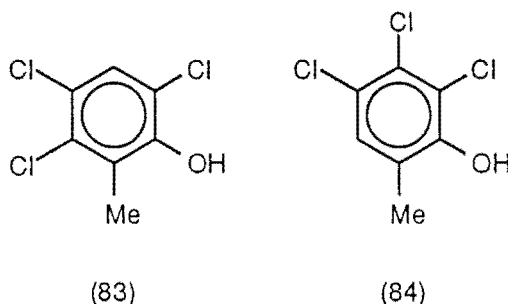
Clearly the PM3 parameter set is unsuitable for this system. It was found in subsequent calculations that the PM3 parameter set failed to accurately model cyclohexadienones with chlorine substituents at C2 as it appears that the method severely underestimates the energy of the *gem*-dichloro moiety. It also appears that the AM1 method suffers this same failing, but to a lesser extent. For dienones with methyl groups at C2 and C6 the PM3 treatment appeared reasonable, but the predicted ratios for 2-chloro-6-methylcyclohexadienones did not correlate well with the experimentally observed values (See Appendix Two).

For this series of reactions it has been assumed that there is no interconversion by [1,5]-sigmatropic shift of chlorine. It is believed that all chlorine addition reactions in this chapter proceed through either the trichloro dienone (63) for Sections 3.1, 3.2 and 3.3, and through the dibromochloro dienone (79) for Sections 3.4 and 3.5.

CHAPTER FOUR

CHLORINATION REACTIONS OF THE TRICHLORO METHYL PHENOLS

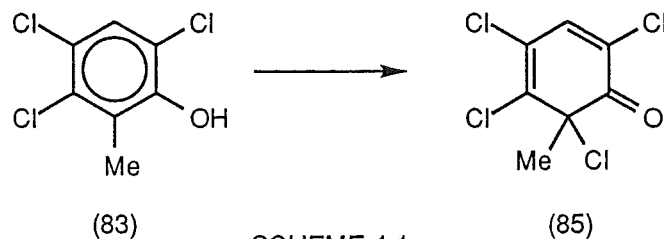
The reactions of trichloro-6-methylphenols were of interest in comparison with the reactions of 2,4-dichloro-6-methylphenol (62) described in the previous chapter. The addition of another chlorine to the ring was expected to make reaction by electrophilic mechanisms less favourable, and verification of this was sought. The reactions discussed in this chapter are for the two phenols, 2,4,5-trichloro-6-methylphenol (83) (Section 4.1.1 to 4.1.5) and 2,3,4-trichloro-6-methylphenol (84) (Section 4.2.1 to 4.2.5).



4.1 The Chlorination Reactions of 2,4,5-Trichloro-6-methylphenol (83):

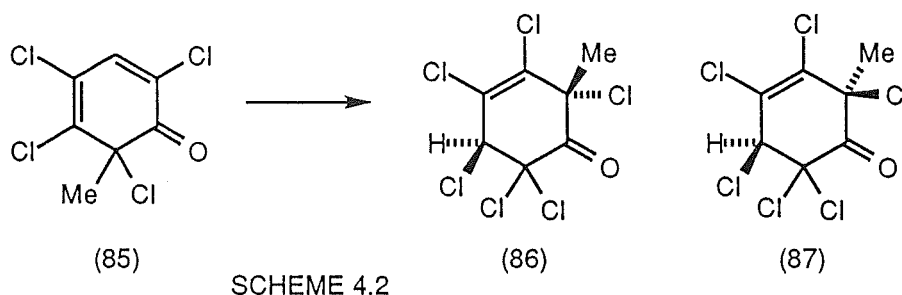
Formation of the tetrachloro dienone (85) was effected by addition of chlorine (1.2 mole equivalents) to a solution of the phenol (83) in carbon tetrachloride containing pyridine. Light was excluded to eliminate free radical side chain chlorinations. (Detailed reaction conditions are set out in the experimental section relating to chapter 4). This reaction gave a single product (Scheme 4.1, over) which was shown to be essentially pure tetrachloro dienone (85), and was identified on the basis of its spectroscopic data. The mass spectrum confirmed the compound was a tetrachloro dienone, and the conjugation pattern was established on the basis of the infrared spectrum (ν_{\max} 1702, 1613, 1551) and ultraviolet spectrum (λ_{\max} 250, 348 nm, ϵ 4800, 1820). The upfield position of the methyl ^1H n.m.r signal (δ 1.971) indicated that this group was attached to a

sp^3 carbon, *ipso* to a chloro substituent rather than attached to an olefinic carbon.



4.1.1 Reaction of Chlorine with 2,4,5,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (85) in Acetic Acid

Reaction of the tetrachloro dienone (85) with chlorine in acetic acid containing hydrochloric acid gave two products, as shown in Scheme 4.2. This reaction was very slow in pure acetic acid, but was complete in two hours when hydrochloric acid was present at a concentration of 0.05 mol l^{-1} .

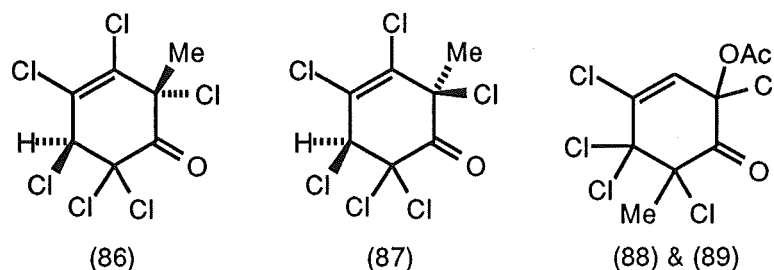


The ratio of the *trans* (86) to *cis* (87) isomers was 3 : 2. The two compounds were separated by chromatography. Both were known compounds and their structures had been assigned earlier on the basis of their spectroscopic data.³⁹

4.1.2 Reaction of Chlorine with 2,4,5,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (85) in Acetic Acid Containing Sodium Acetate

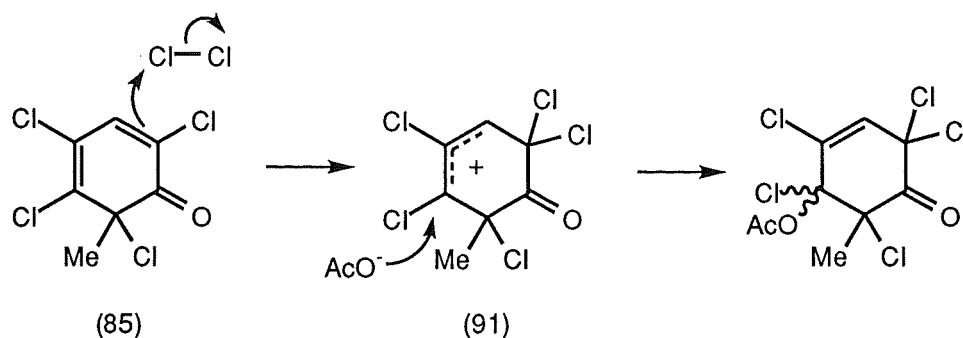
Addition of sodium acetate to the solvent slowed the rate of chlorine addition to the tetrachloro dienone (85) such that the reaction time for complete conversion was extended from two hours to 14 days. The reaction gave the two

hexachloro ketones (86) and (87) in yields of 9% and 18% respectively, plus the two acetoxy compounds (88) and (89) in yields of 42% and 31% respectively (Scheme 4.3). The latter two could not be separated from each other and their structures are assigned tentatively on the basis of mechanistic considerations and on the ^1H n.m.r. spectrum of the mixture.

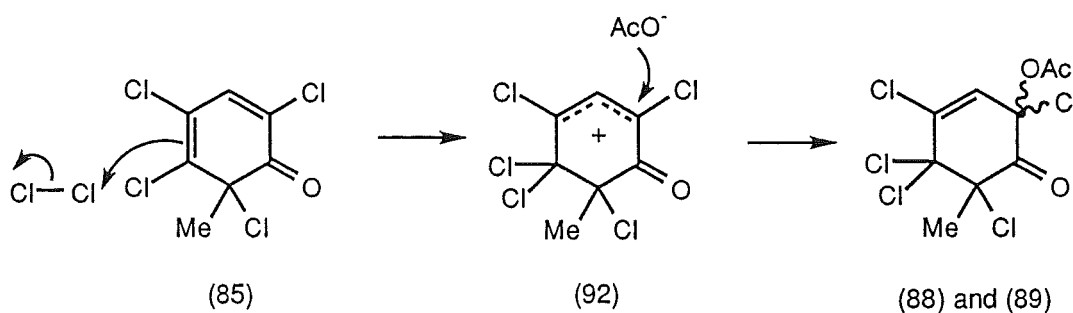


SCHEME 4.3

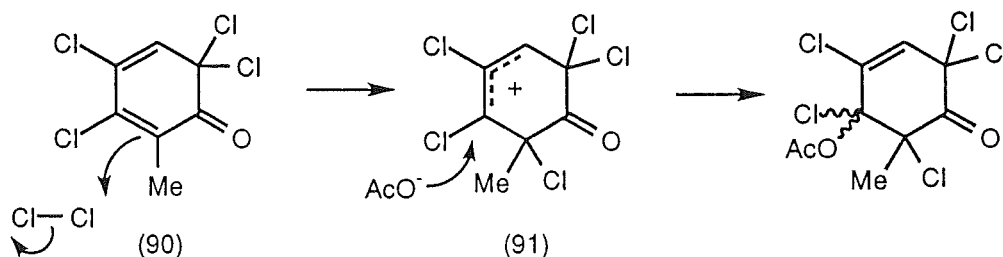
The ^1H n.m.r. spectrum of the mixture showed that the downfield proton of compound (88) occurred at δ 6.125, and that of compound (89) occurred at δ 6.215. These are indicative of cyclohex-3-enone structures with the proton attached at C3 in both cases. This structural feature can form only by the three electrophilic routes shown below (Scheme 4.4). As the solvent contains sodium acetate, significant addition by nucleophilic pathways is unlikely. The first two mechanisms (Scheme 4.4a and 4.4b, over) occur by initial chlorine attack to either C2 or C5 of the tetrachloro dienone (85). The initial step in the third mechanism (Scheme 4.4c, over) is chlorine attack at C2 of the tetrachloro dienone (90) formed by a [1,5]-sigmatropic shift of chlorine from the tetrachloro dienone (85).



SCHEME 4.4a



SCHEME 4.4b



SCHEME 4.4c

It should be noted that the first and third mechanisms proceed through the same intermediate (91) and would give the same products.

Semi-empirical calculations using the AM1 parameter set in the MOPAC program confirmed the belief that the intermediate (92) would be more stable than the intermediate (91). Heats of formation for the two were calculated as 753 kJ mol⁻¹ for (91) and 720 kJ mol⁻¹ for (92). This favours the second mechanism (Scheme 4.4b).

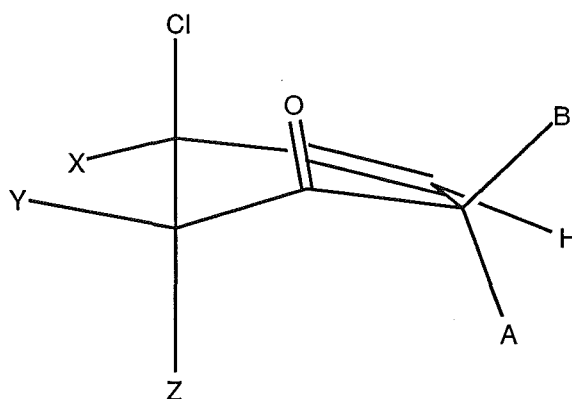
Also supporting the second mechanism is the observation that formation of the products by the first and third mechanisms (Schemes 4.4a and 4.4c) requires the less likely attack on the intermediate (91) by acetate ion at C5, *ipso* to a chloro substituent, rather than at the unsubstituted C3. In contrast, in Scheme 4.4b attack of acetate ion could occur potentially at either C2 or C4 both of which carry chlorine substituents; the proposed attack at C2 is consistent with the apparent preference (e.g. Section 3.3) for nucleophilic attack at C2 in such circumstances.

The ^1H n.m.r. spectrum of the mixture of the two acetates (88) and (89) is as follows:

(88) δ 6.125 (H3), 2.132 (OCOMe), 2.026 (6-Me)

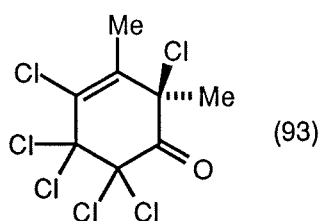
(89) δ 6.215 (H3), 2.166 (OCOMe or 6-Me), 2.161 (OCOMe or 6-Me)

It is usual in cyclohex-3-enones for the alicyclic ring to adopt a twist boat conformation with the C5-chloro substituent in the axial position. This dictates the orientation of the other C5-substituent and also the positioning of the C2 and C6 substituents. As can be seen from the figure below, the C5 substituents occupy the axial and equatorial position. The preferred orientation of the C6-substituents is similar to this, with the C6-axial substituent (Z) *anti* to the C5-axial chlorine. The C6-equatorial substituent (Y) is in a *gauche* configuration with the two C5 substituents.



The substituents of the other sp^3 centre C2 (A and B), are close to equally spaced above and below the ring with respect to H3. It has been demonstrated that the size of these substituents has little effect on the ring conformation.²³

The introduction of another chlorine to C5 can lead to 'flipping' of the ring as each chlorine atom in turn occupies the axial position, and this was illustrated in compound (93).²⁹



The ^1H n.m.r. spectrum of compound (93) at 55° gave a time-averaged spectrum with signals at δ 1.97 (2-Me) and 2.20 (3-Me). On cooling to -12° , the 2-Me protons gave rise to signals at δ 1.89 and 2.13, while the 3-Me protons appeared as a sharp singlet at δ 2.20. This 'flipping' was also trapped out in the solid state, and two conformations of this compound were seen in the X-ray structure. The best model for the diffraction data consisted of non-stoichiometric disordering of the substituent atoms C(7) and Cl(2) about the carbon atom C(2). The calculated site-occupancy factors were 0.85 for the atoms C(7) and Cl(2) in the positions represented by Figure 4.1a, and 0.15 for the disordered atoms C(7') and Cl(2') in the positions represented by Figure 4.1b.

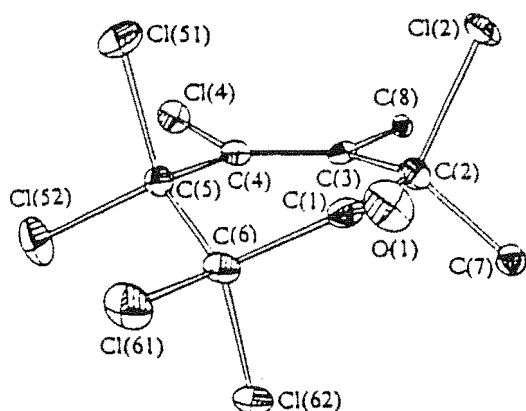


Figure 4.1a

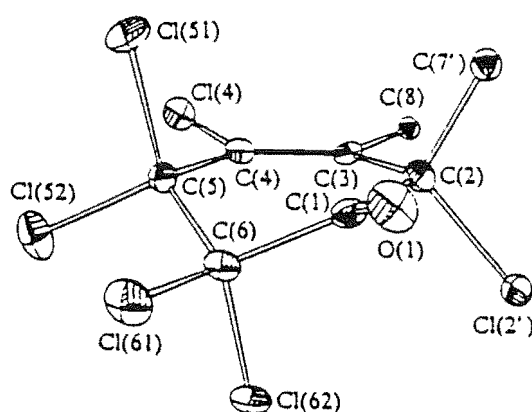


Figure 4.1b

Perspective Drawing of Compound (93)

In the absence of closely related compounds it is not possible to predict the preferred conformation of the acetoxy compounds (88) and (89), or whether they will be conformationally mobile. Unfortunately, as these compounds are not crystalline structure analysis by X-ray crystallography is not possible.

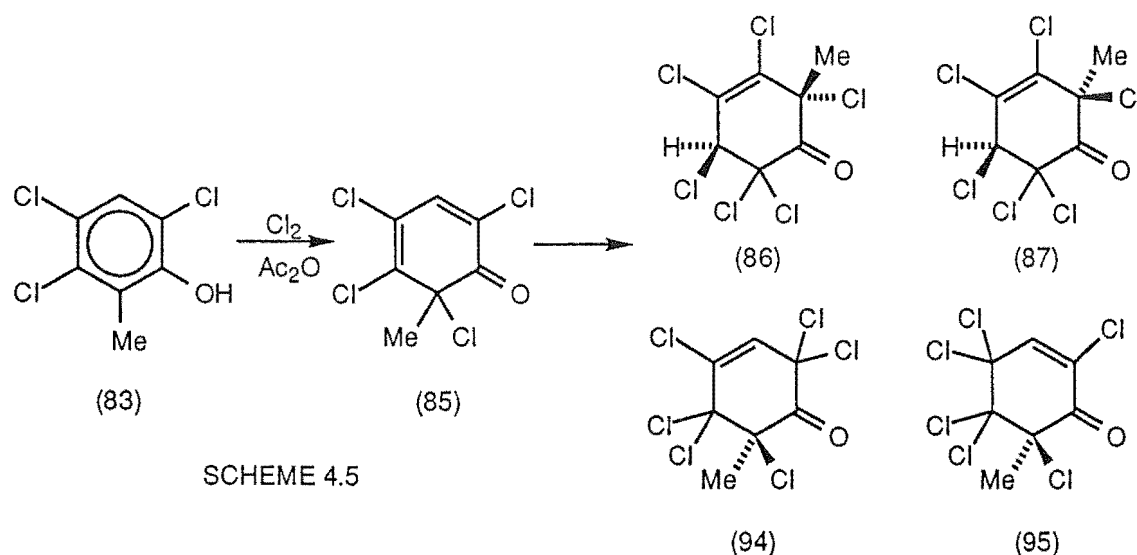
A possible, but unlikely, route to the formation of acetate compounds (88) and (89) was a rearrangement of the hexachloro ketones (86) and (87) in the presence of sodium acetate. To exclude this, a solution of the two hexachloro

ketones was stirred in acetic acid containing sodium acetate for 14 days. After this time there was no evidence of either of the acetates (88) or (89).

To discount the possibility that the acetate compounds were not addition products, but substitution products, a solution of the tetrachloro dienone (85) and sodium acetate in acetic acid was stirred for 14 days. As above, at the end of this time there was no evidence of the acetates (88) and (89).

4.1.3 Reaction of Chlorine with 2,4,5-Trichloro-6-methylphenol (83) in Acetic Anhydride

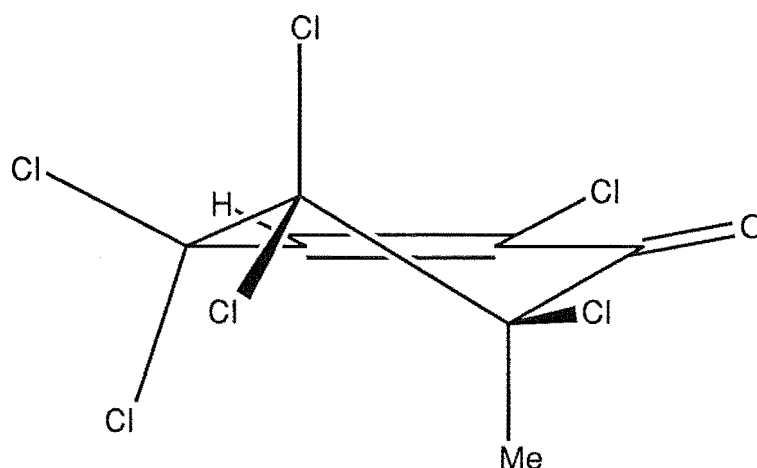
Addition of chlorine to the trichloro phenol (83) in acetic anhydride proceeded rapidly to form the tetrachloro dienone (85); after 15 minutes no phenol remained. However addition of chlorine to the dienone (85) was extremely slow. After 3 days only 40% had reacted to give a mixture of the two hexachloro ketones (86) and (87) and two new compounds (94) and (95) (Scheme 4.5). The mixture was separated by chromatography.



The two hexachloro ketones (86) and (87) (with yields 10% and 25% respectively) were eluted first and identified by comparison with authentic material (Section 4.1.1).

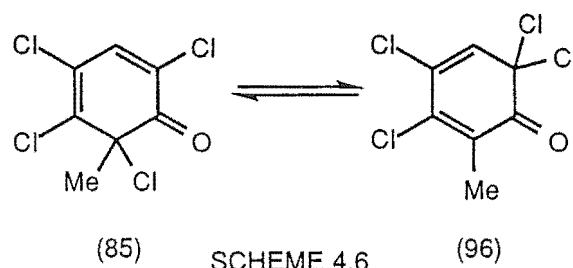
The third compound to be eluted was the cyclohex-3-enone (94) (44%), and its structure was assigned on the basis of its spectroscopic data. The mass spectrum confirmed the molecular formula, and the infrared spectrum indicated a non-conjugated cyclohexenone. The position of the downfield proton in the ^1H n.m.r. spectrum (δ 6.527) showed it to be olefinic with attachment at C3. The methyl signal occurred downfield (δ 2.171) due to deshielding by a chloro substituent. A methyl group in the equatorial position would be expected to display a ^1H n.m.r signal *c.* δ 0.2 upfield; thus the C6-methyl group exists in the axial position, where it is deshielded by the axial C2-chlorine.

The last compound to be eluted was the conjugated ketone (95) (21%), and its structure was assigned on the basis of its spectroscopic data. The infrared spectrum (ν_{max} 1720, 1612) and the ultraviolet spectrum (λ_{max} 252 nm, ϵ 8760) indicate the conjugation pattern. This was supported by the downfield position of the olefinic proton (δ 7.397) which must be attached to C3. The downfield position of the methyl signal of compound (95) (δ 2.165) indicates that this group exists in the axial position, and is deshielded by the axial C4-chlorine, as shown below.



4.1.4 Semi-Empirical Calculations of a Possible Dienone Interconversion

Only the 2,4,5,6-tetrachloro dienone (85) was observed experimentally, no 3,4,6,6-tetrachloro dienone (96) being observed (Scheme 4.6). However, it was considered important to explore the energetics of the possible intermediacy of the 3,4,6,6-tetrachloro dienone (96).



The AM1 parameter set was used in the program MOPAC to calculate the heats of formation of the two dienones. These were found to be (85) $-112.6 \text{ kJ mol}^{-1}$ and (96) $-111.2 \text{ kJ mol}^{-1}$. Application of a Boltzmann distribution gives a ratio of 64 : 36 at 22° . As mentioned in Section 3.8, the method appears to underestimate the energy of the *gem*-dichloro moiety which leads to the above ratio not matching the experimentally observed figure [(85) : (96) 100 : 0] (See Appendix Two).

The heat of formation of the transition state was also calculated. An appropriate transition state structure was determined and refined using the gradient minimisation procedure in the MOPAC program. Vibrational analysis revealed a single negative eigenvalue, which indicates the structure represents a saddle point on the potential energy surface. The heat of formation was calculated as being 54.2 kJ mol^{-1} . The geometry of the transition state is shown in Figure 4.2 (over). The chlorine is slightly closer to C2, the carbon bearing a chloro substituent, than C6, the carbon bearing the methyl group (2.30\AA and 2.32\AA respectively).

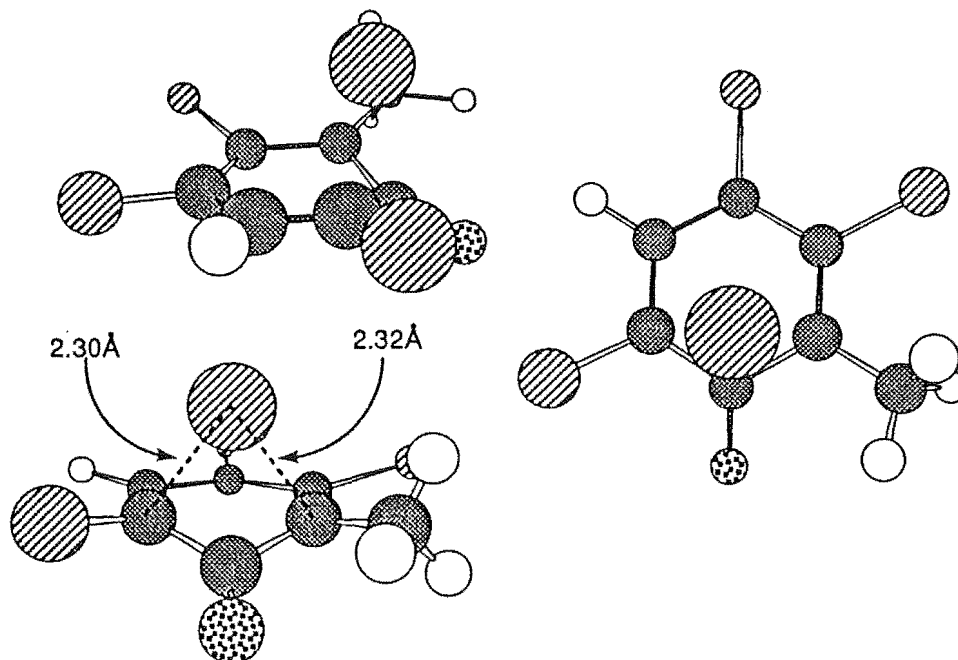


Figure 4.2 AM1 Calculated Geometry of the Transition State in the Interconversion of the Tetrachloro Dienones (85) and (96)

The barrier to interconversion of the tetrachloro dienone (85) to (96) is similar to the value for other dienone interconversions (Section 2.4 and 3.8) at $166.8 \text{ kJ mol}^{-1}$.

A potential energy hypersurface was calculated for C2-chlorine and C6-chlorine distances ranging from 1.5 Å to 3.6 Å , and is presented in Figure 4.3.

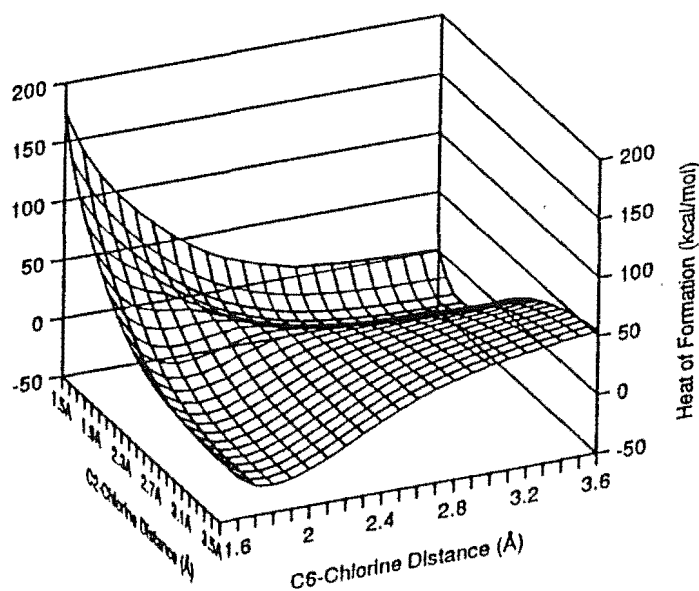


Figure 4.3 AM1 Calculated Potential Energy Hyper-Surface

As in Section 2.4, no unusual features appear on the surface. The two dienones exist at the ends of the valleys, and the transition state lies at the saddle point between these.

The PM3 parameter set was also used to calculate the heat of formation of the two dienones and the barrier to interconversion as a comparison. The values calculated were, for (85) $-140.5 \text{ kJ mol}^{-1}$, for (96) $-141.6 \text{ kJ mol}^{-1}$, and for the transition state 0.6 kJ mol^{-1} . These figures lead to a Boltzmann distribution of (85) : (96) of 39 : 61 at 22° and a barrier to the conversion of (85) to (96) of $141.1 \text{ kJ mol}^{-1}$. The value for the interconversion barrier is similar to those found for the trichloro dimethyl dienones (48) and (49) ($138.8 \text{ kJ mol}^{-1}$, Section 2.4) and the trichloro methyl dienones (63) and (82) ($139.1 \text{ kJ mol}^{-1}$, Section 3.8) (See Appendix Two).

This pair of tetrachloro dienones (85) and (96) is yet another illustration of the failing of the AM1 and PM3 treatments of the *gem*-dichloro moiety. No 3,4,6,6-tetrachloro dienone (96) was observed experimentally, yet the predicted value was 36% by AM1, or 61% by PM3.

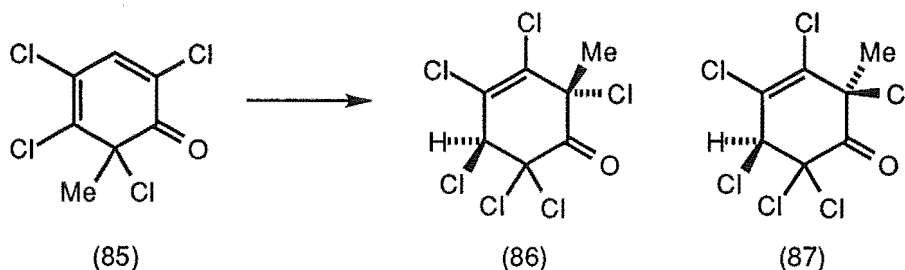
It is believed in this section of work that the interconversion of (85) and (96) is not occurring, and that the reactions discussed in this section proceed from the 2,4,5,6-tetrachloro dienone (85).

4.1.5 Discussion

(a) Reactions in Acetic Acid

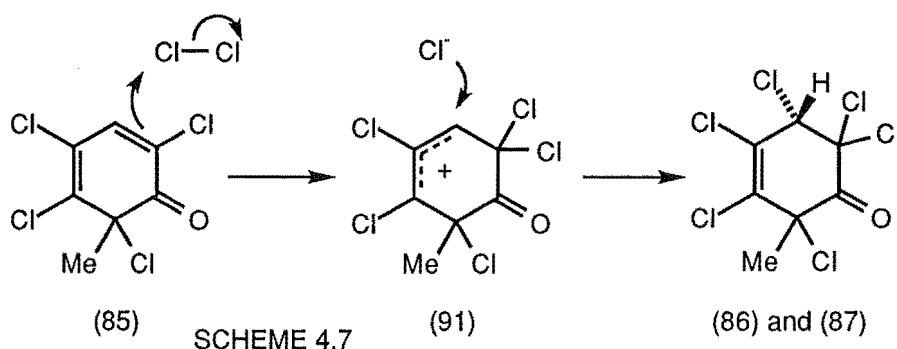
The tetrachloro dienone (85) reacts with chlorine in acetic acid by nucleophilic mechanisms to give the hexachloro ketones (86) and (87). Addition of species to remove chloride ion, believed to be necessary for the nucleophilic addition

pathways, all but stops the reaction. With added sodium acetate the half life of the the reaction increases from less than 15 minutes to something of the order of 35 hours, and in acetic anhydride it is around 90 hours. The hexachloro ketones (86) and (87) form by 2,3-addition to the tetrachloro dienone (85). The *gem*-6,6-dichloro moiety restricts the acquisition of information about the stereochemistry of this addition.

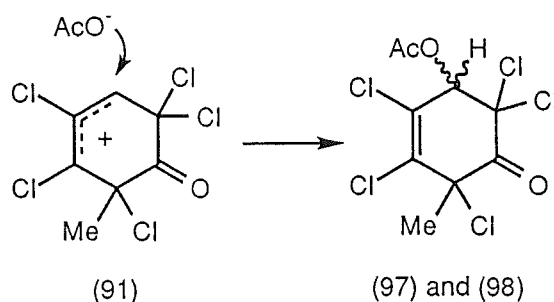


(b) Reactions in Acetic Acid Containing Sodium Acetate

Chlorine addition to the tetrachloro dienone (85) in acetic acid containing sodium acetate gave the two hexachloro ketones (86) and (87) and the two acetoxy compounds (88) and (89). The mode of formation of the acetoxy compounds is by chlorine attack at C5 followed by nucleophilic attack on the cation (92) by acetate ion at C2, as discussed in Section 4.1.2. As in the reactions in acetic anhydride (Section 4.1.3) some 2,3-addition is occurring to this dienone to give the hexachloro acetates (86) and (87) (total yield 27%). Sodium acetate should suppress most nucleophilic addition, so that if the hexachloro ketones (86) and (87) are forming by electrophilic pathways initial chlorine attack will occur at C2 to give the delocalised cation (91) and a chloride ion in a intimate ion pair. Nucleophilic attack at C2 generates the observed products (86) and (87) (Scheme 4.7).



It was postulated at an early stage that the intermediate (91) might be captured by acetate ion to give the alternative structures, (97) and (98) for the acetoxy compounds (88) and (89).



However, following the establishment of the structures for the epimeric acetates (88) and (89), it is now believed that the intimate ion pair of the intermediate (91) and the chloride ion react rapidly, precluding the possibility of external acetate ion attack leading to acetoxy structures (97) and (98).

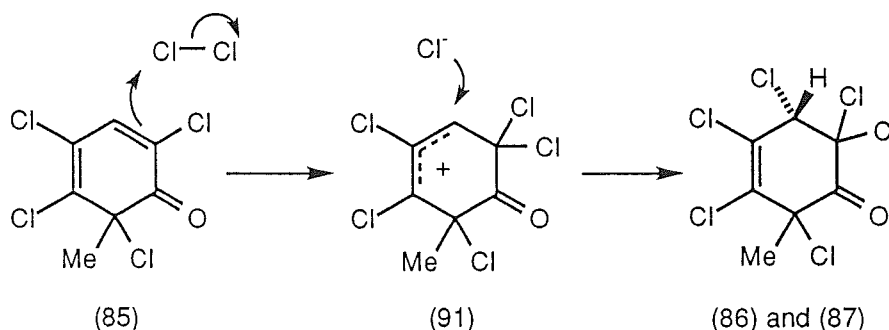
The possibility exists that the hexachloro ketones (86) and (87) arise through incomplete suppression of nucleophilic addition to the tetrachloro dienone (85). It has been demonstrated that sodium acetate is not wholly effective in blocking nucleophilic addition (Sections 3.2 and 3.7). The total yield of compounds (86) and (87) is 27% compared with Section 3.2 where 18% of the total yield was formed by residual nucleophilic addition. If the dienone (85) is reacting by these pathways the higher yield is believed to be a reflection of the extended reaction time, and the fact that nucleophilic addition should be more favoured for this dienone due to the location of the electron withdrawing chlorine substituents. The four chlorines on the dienone ring will lower the electron density of the π -system disfavoured electrophilic addition. This will make the alternative nucleophilic reaction pathways more attractive.

The observation that the hexachloro ketones (86) and (87) are formed in the reactions in acetic anhydride indicates that initial chlorine attack at C2 of the

tetrachloro dienone (85) leading to the formation of (86) and (87) is almost as favourable as attack at C5 to form the cyclohex-3-enone (94) and conjugated ketone (95). This provides support for the formation of (86) and (87) in acetic acid containing sodium acetate by electrophilic 2,3-addition.

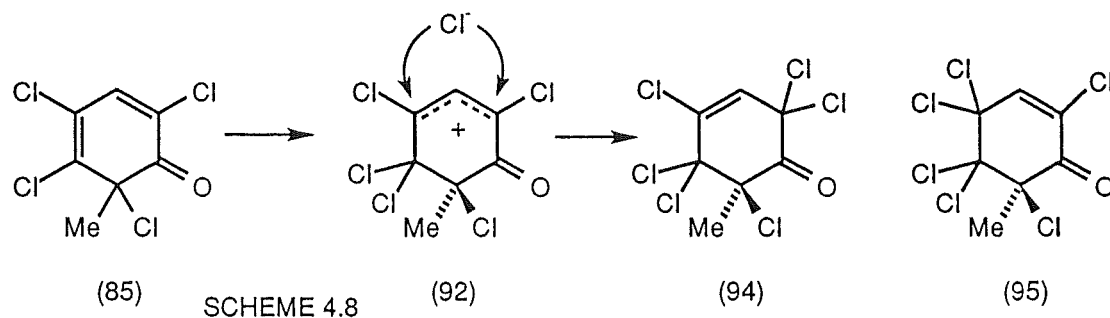
(c) Reactions in Acetic Anhydride

Addition of chlorine to the tetrachloro dienone in acetic anhydride was very slow, indicating that electrophilic addition of chlorine is unfavourable to this dienone. It is believed that the two 2-methyl ketones (86) and (87) are formed as shown below, namely attack at C2 of the tetrachloro dienone (85) by chlorine to give the cation (91) and chloride ion, in an ion pair, followed by capture by chloride ion at C3 to give the observed products.



Capture of (91) at C5 instead of C3 by chloride ion would generate the cyclohex-3-enone (93). This ion pair clearly reacts rapidly, precluding nucleophilic attack by acetate ion to give acetoxy products. As is typical for this solvent *cis* addition is favoured (*cis* (87) : *trans* (86) = 5 : 2).

The two 6-methyl ketones (94) and (95) form presumably by attack at C5 of the tetrachloro dienone (85) to give the cation (92) (Scheme 4.8, over), followed by capture by chloride ion at either C2 to give (94) or at C4 to give (95). The relative yields of these two reflect the apparent preference for nucleophilic attack at C2 in such circumstances.



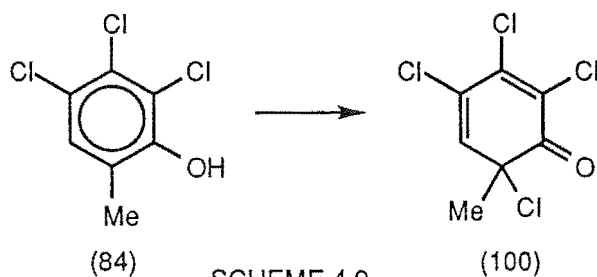
As the cation (92) will be more stable than the cation (91), the intermediate in the formation of the 2-methyl ketones (86) and (87), (Section 4.1.2) the combined yield of the 6-methyl ketones (94) and (95) is higher. However, the reasonable yield of the two 2-methyl ketones (86) and (87) (14%) compared with the two 6-methyl ketones (93) and (94) (27%) is a reflection of the steric effects encountered during the initial chlorine attack. Compounds (86) and (87) form by initial attack at the less hindered C2 site, whereas (93) and (94) require initial attack at C5, adjacent to a chlorine at C4 and methyl group and chlorine at C6.

The high yield of unreacted tetrachloro dienone after three days reflects its lack of reactivity towards molecular chlorine by electrophilic reaction pathways.

In summary, the tetrachloro dienone (85) has a marked preference for reaction by nucleophilic mechanisms. It is believed that incomplete suppression of nucleophilic addition pathways may be occurring in the sodium acetate reaction. The compounds (86) and (87) (total yield 27%) could form by these routes, or by electrophilic addition involving an intimate ion pair which prevents the formation of acetate products. This reaction took 14 days for completion compared with 2 hours for the reaction without sodium acetate. The reaction in acetic anhydride was slower still. With a half life of around 90 hours, it would take over 30 days for complete reaction. The products in this reaction arise solely by electrophilic pathways, either 2,3-addition [(86) and (87)], or 2,5-addition (94) or 4,5-addition (95).

4.2 The Chlorination Reactions of 2,3,4-Trichloro-6-methylphenol (84):

The formation of the tetrachloro dienone (100) occurred in the usual manner. The reaction gave a single product (Scheme 4.9), which was identified on the basis of the spectroscopic data as being 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100).

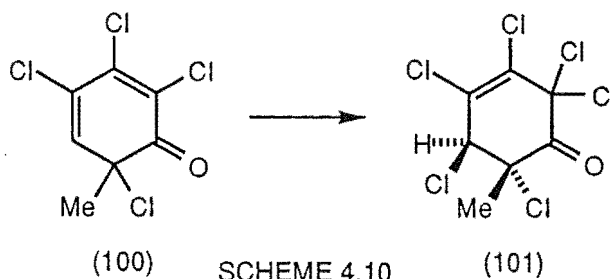


SCHEME 4.9

The mass spectrum confirmed the molecular formula, and the infrared (ν_{\max} 1685, 1611, 1531) and ultraviolet (λ_{\max} 332, 246, 216 nm ϵ 1480, 5090, 7580) spectra indicated a cyclohexa-2,4-dienone structure. The ^1H n.m.r. spectrum indicated a methyl group (δ 1.846) *ipso* to a chlorine, and the presence of an olefinic proton (δ 6.615) at C5.

4.2.1 Reaction of Chlorine with 2,3,4,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (100) in Acetic Acid

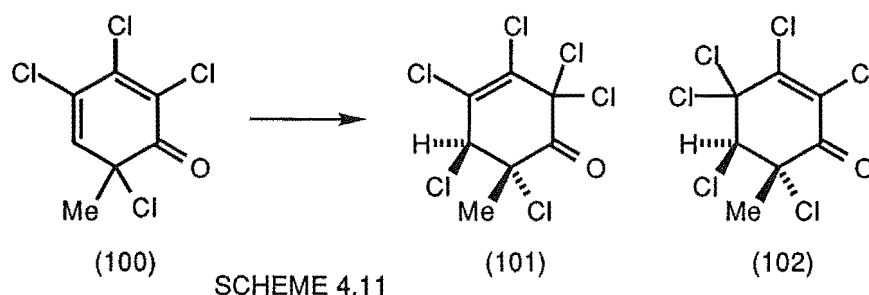
Reaction of the dienone (100) with chlorine in acetic acid was slow, taking 14 days for completion. The reaction gave a single product (101) (Scheme 4.10), which was a known compound and its structure had been determined by single crystal X-ray analysis.²⁵



SCHEME 4.10

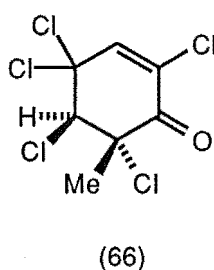
4.2.2 Reaction of Chlorine with 2,3,4,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (100) in Acetic Acid Containing Sodium Acetate

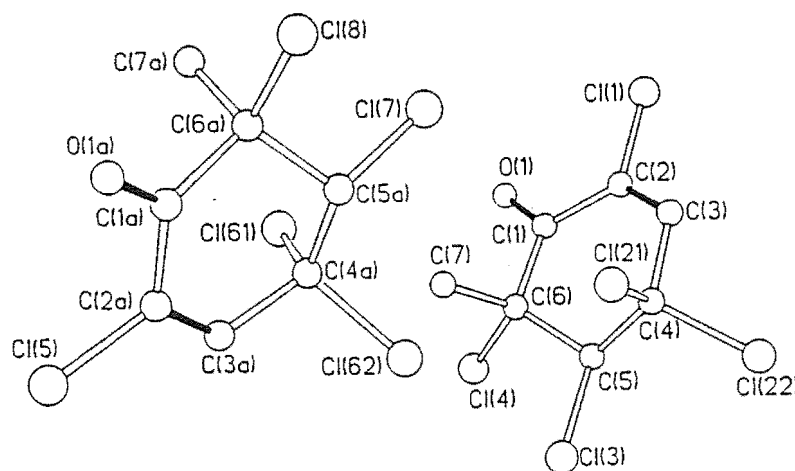
Addition of sodium acetate to the solvent slowed the reaction further. After 14 days only 51% of the tetrachloro dienone (100) had reacted to give a mixture of two compounds (Scheme 4.11). These were separated by chromatography.



The first compound to be eluted was the cyclohex-3-enone (101) (57%), identical with authentic material (Section 4.2.1).

The other compound was the conjugated ketone (102) (43%), and its structure was assigned on the basis of its spectroscopic data. The mass spectrum indicated a hexachloromethylcyclohexenone and the infrared (ν_{\max} 1719, 1675) and ultraviolet (λ_{\max} 256, 214, ϵ 10990, 4830) spectra confirmed the conjugation. The similarities of the ^1H n.m.r. spectrum of this compound (δ 5.110, 1.911) with the H5 and methyl signals of the conjugated ketone (66) (δ 5.031, 1.887), the structure of which was determined by single crystal X-ray analysis (over), indicate that compound (102) adopts a similar conformation. This implies that H5 and the C6-methyl group adopt axial orientations.

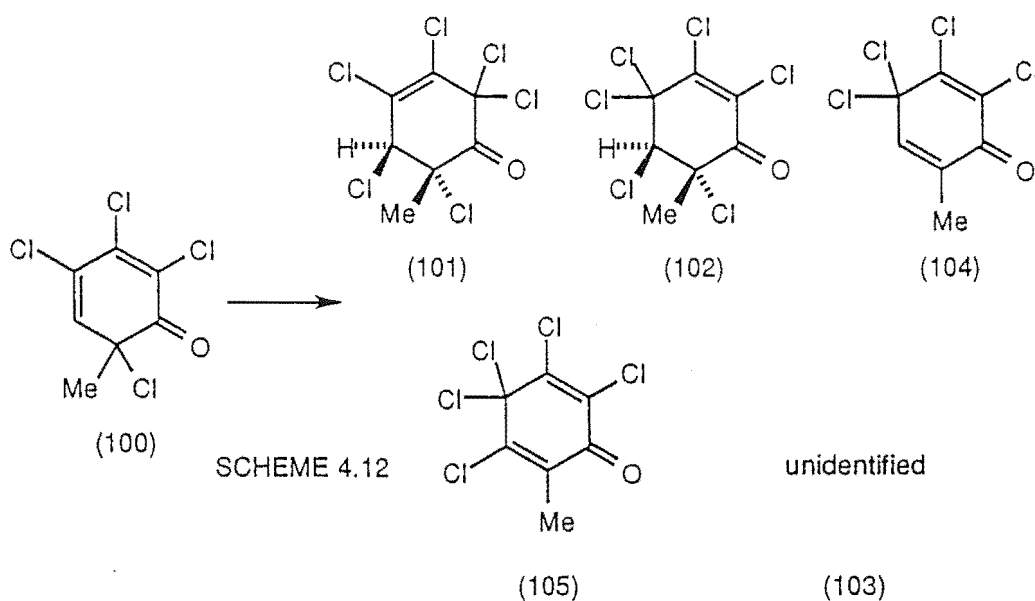




Perspective Drawing of Compound (66)

4.2.3 Reaction of Chlorine with 2,3,4,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (100) in Acetic Anhydride

The reaction in acetic anhydride occurred rapidly compared with the reactions in acetic acid and acetic acid/sodium acetate. After four hours no tetrachloro dienone (100) remained. The reaction gave a mixture of five compounds (Scheme 4.12) which were separated by chromatography.



The first compound to be eluted was the cyclohex-3-enone (101) (49%), identical with authentic material (Section 4.2.1).

The second compound eluted (103) (5%) could not be identified on the basis of the spectroscopic data. The infrared (ν_{\max} 1712, 1573) and ultraviolet (λ_{\max} 273, ϵ 6150) spectra indicate a conjugated ketone. The ^1H n.m.r. spectrum shows a methyl group *ipso* to a chlorine (δ 1.940), but the downfield proton occurs at δ 4.201, which is too far upfield to be olefinic or *ipso* to a chlorine substituent. A signal in this position would be consistent for a proton *ipso* to acetoxy or hydroxy groups, but there was no evidence in the infrared and ^1H n.m.r. spectra of either of these. A parent ion could not be located by mass spectroscopy, and the compound was too unstable to allow the growing of crystals suitable for X-ray crystallography.

The third compound eluted was the cyclohexa-2,5-dienone (104) (13%), and its structure was assigned on the basis of its spectroscopic data. The mass spectrum confirmed that this compound was a tetrachloro dienone, and the infrared and ultraviolet spectra showed that this was a cyclohexa-2,5-dienone. The ^1H n.m.r. showed allylic coupling from H5 (δ 7.061) to the C6-methyl group (δ 2.044) (J 1.5Hz). The downfield position of both of these signals indicates attachment to olefinic carbons. The ultraviolet spectrum showed a λ_{\max} value of 252 nm with a log ϵ of 3.92, typical for cyclohexa-2,5-dienones. Only one C=C vibration was observed in the infrared (ν_{\max} 1677, 1586) whereas two are normally seen for cyclohexa-2,4-dienones.

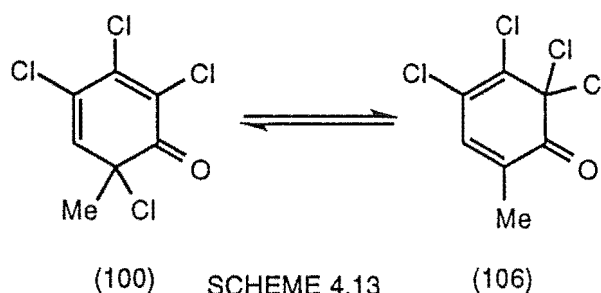
The next compound to be eluted was the conjugated ketone (102) (13%), identical with authentic material (Section 4.2.2).

The last compound eluted is the pentachlorocyclohexa-2,5-dienone (105) (5%), and its structure was assigned on the basis of its spectroscopic data. A parent

ion could not be located by mass spectroscopy. The infrared spectrum (ν_{\max} 1690, 1667), and the observation that the carbonyl carbon signal occurs upfield of δ 190 in the ^{13}C n.m.r indicate a cyclohexa-2,5-dienone structure. There is only one signal in the ^1H n.m.r spectrum (δ 2.298), indicative of an olefinic methyl group. The ultraviolet spectrum contains two absorptions above 250 nm (λ_{\max} 282, 274 nm, ϵ 12410, 9570), yet it is typical for cyclohexa-2,5-dienones to display the π - π^* transition below this wavelength. However, it is known that polar olefinic substituents shift this absorption to higher wavelengths.⁴⁷

4.2.4 Semi-Empirical Calculations of a Possible Dienone Interconversion

The tetrachloro dienone (106) was studied by semi-empirical calculations to investigate the possibility that a [1,5]-sigmatropic shift might be occurring in the reaction of the 2,3,4,6-tetrachloro dienone (100) with chlorine. Although the 4,5,6,6-tetrachloro dienone (106) was not observed experimentally the energetics of the system were of interest.



The AM1 parameter set was used in the program MOPAC to calculate the heats of formation of the two cyclohexa-2,4-dienones (100) and (106) and of the transition state of the interconversion. The values for the tetrachloro dienones were $-112.63 \text{ kJ mol}^{-1}$ and $-111.25 \text{ kJ mol}^{-1}$ for (100) and (106) respectively. This corresponds to a Boltzmann distribution ratio of 64 : 36 for (100) : (106) at 22° . The heat of formation for the transition state was calculated as being 55.4 kJ mol^{-1} . This gives a barrier to conversion of (100) into (106) of $168.0 \text{ kJ mol}^{-1}$.

The geometry of the AM1 calculated transition state is presented in Figure 4.4. The chlorine is slightly closer to C2, the carbon bearing the chloro substituent than C6 the carbon bearing the methyl group (2.31 Å vs. 2.32 Å respectively). This is very similar to the geometry of the transition state calculated for the interconversion of the 2,4,5,6-tetrachloro dienone (85) to the 3,4,6,6-tetrachloro dienone (96) in Section 4.1.4 (See Appendix Two).

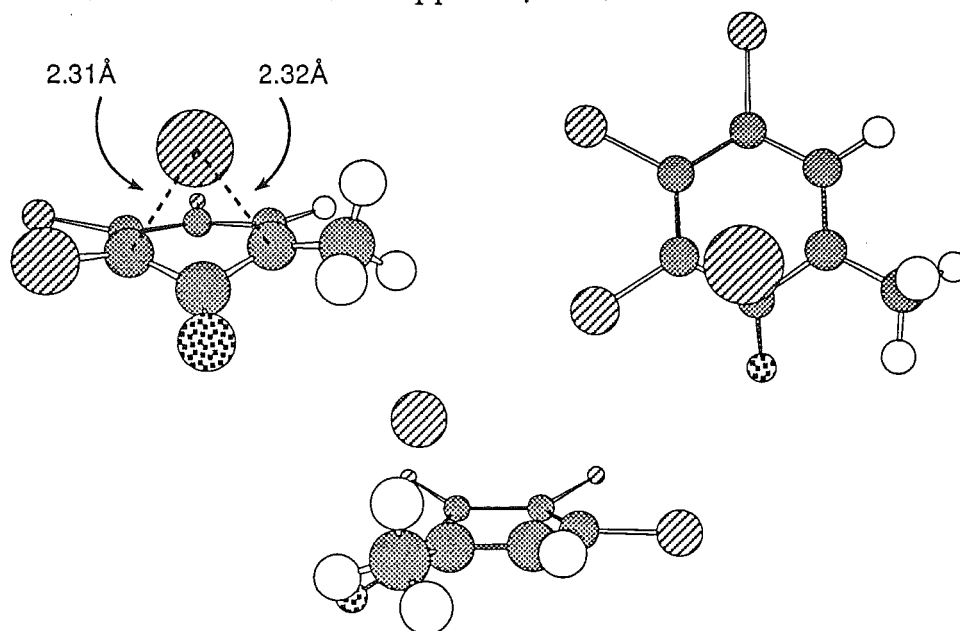


Figure 4.4 AM1 Calculated Geometry of the Transition State in the Interconversion of the Tetrachloro Dienones (100) and (106)

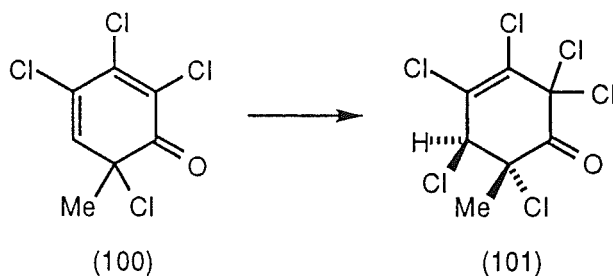
The calculated energy of the barrier to interconversion of the two dienones (100) and (106) of $168.0 \text{ kJ mol}^{-1}$ is similar to that for other dienone interconversions by a [1,5]-sigmatropic shift, for example Section 4.1.4 $166.8 \text{ kJ mol}^{-1}$, Section 2.4 $164.6 \text{ kJ mol}^{-1}$, and Section 3.8 $166.3 \text{ kJ mol}^{-1}$. As mentioned in Section 3.8, even though this value is of a similar magnitude to the interconversion of the two trichloro dimethyl dienones (48) and (49) (Section 2.4) which are known to interconvert, and a Boltzmann distribution ratio of 64 : 36 for (100) : (106) is predicted, only the 2,3,4,6-tetrachloro dienone (100) is observed experimentally.

In spite of the outcome of the calculations, above, it is believed that for the pair of tetrachloro dienones (100) and (106), the [1,5]-sigmatropic shift is not occurring, and the chlorine addition reactions proceed through the 2,3,4,6-tetrachloro dienone (100) only.

4.2.5 Discussion

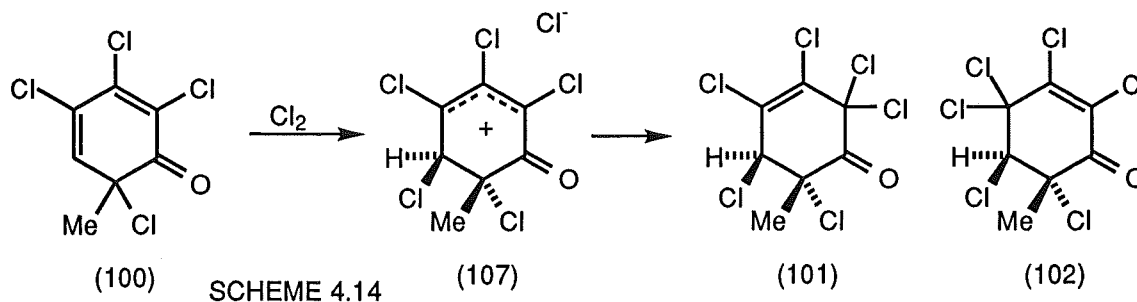
(a) Reactions in Acetic Acid

Addition of chlorine to the tetrachloro dienone (100) occurs slowly in acetic acid to give the cyclohex-3-enone (101). It is not known whether this is occurring by electrophilic or nucleophilic addition. The reaction was slowed considerably by addition of sodium acetate to the solvent; this implies that addition in acetic acid occurs by nucleophilic mechanisms, and suppression of these pathways by removal of chloride ion virtually halts the reaction. Addition does occur but is very slow. However, this is contradicted by the observation that the reaction in acetic anhydride proceeds to completion in less than four hours. For this reason the nature of the 2,5-addition occurring to form the cyclohex-3-enone (101) is not known.



(b) Reactions in Acetic Acid/Sodium Acetate

The reaction in acetic acid/sodium acetate was extremely slow, after two weeks only half of the dienone had reacted. The products are believed to form by initial electrophilic attack of chlorine at C5 of the tetrachloro dienone (100) to give the delocalised intermediate (107) (Scheme 4.14, over).

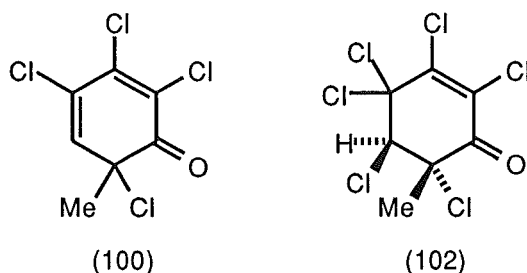


Although the C2 and C4 chloro substituents stabilise the positive charge by resonance donation of electrons, the C3 chlorine will destabilise this cation by inductive electron withdrawing effects. The difficulty of formation of the cationic intermediate (107) is believed to be responsible for the rate of reaction being so slow. Attack on the intermediate (107) at either C2 or C4 by chloride ion generates the two products (101) and (102) respectively. The formation of these two compounds as major products in the reaction in acetic anhydride indicates that reaction of the tetrachloro dienone (100) with chlorine by electrophilic addition, as shown above, is not an unreasonable reaction pathway for this system. The lack of acetoxy products from this reaction can be rationalised in terms of the formation of the cationic intermediate (107) in an intimate ion pair with chloride ion; reaction of this intimate ion pair would be expected to occur more rapidly than attack by external acetate ion.

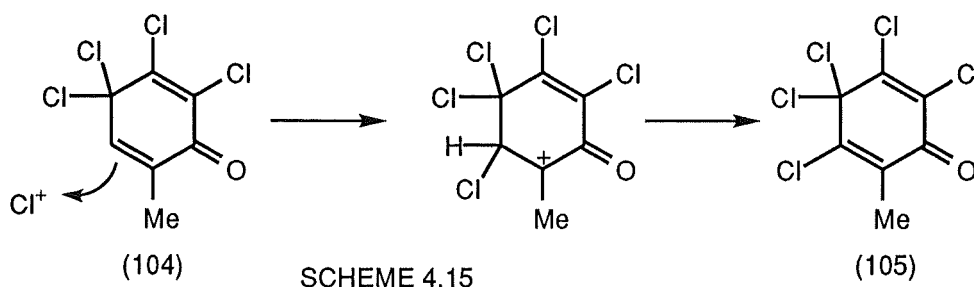
(c) Reaction in Acetic Anhydride

The major products in the reaction of the tetrachloro dienone (100) with chlorine in acetic anhydride are the cyclohex-3-enone (101) and the conjugated ketone (102). These two form by electrophilic addition to the dienone (100), *via* the delocalised cation (107), as shown in Scheme 4.14 (above). The *gem*-dichloro moieties in each of these compounds obscures the stereochemistry of the chlorine addition, but in this solvent this is likely to occur *cis*, as explained in Section 2.1.4.

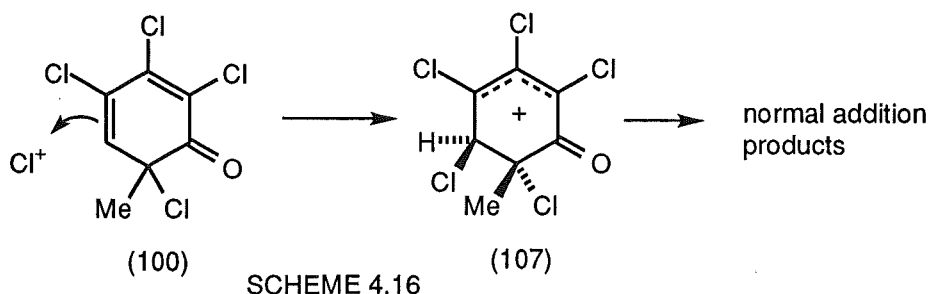
The tetrachlorocyclohexa-2,5-dienone (104) could form by two routes, either by loss of Cl_2 across C5/C6 of the conjugated ketone (102) or by a shift of chlorine from C6 to C4 of the tetrachlorocyclohexa-2,4-dienone (100). Likewise it was thought that the pentachloro cyclohexa-2,5-dienone (105) could form by loss of HCl across C5/C6 of the conjugated ketone (102). To further investigate the mode of formation of these two cyclohexa-2,5-dienones (104) and (105), samples of the conjugated ketone (102) and the tetrachloro dienone (100) were stirred in acetic anhydride at -10° for four hours. The tetrachlorocyclohexa-2,5-dienone (104) was found in both cases, in yields of 4% from the tetrachlorocyclohexa-2,4-dienone (100) and 8% from the conjugated ketone (102).



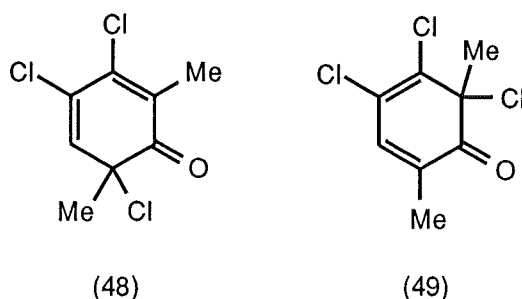
The pentachlorocyclohexa-2,5-dienone (105) was not produced by treatment of the conjugated ketone (102) with acetic anhydride. However, this dienone (105) was found after stirring the tetrachloro dienone (100) in acetic anhydride (10%) along with a small amount of 2,3,4-trichloro-6-methylphenol (84). This implies the tetrachloro dienone (100) is disproportionating, giving Cl^+ and the trichloro phenolate ion, which gains a proton from the solvent. Capture of the Cl^+ ion by the tetrachlorocyclo-2,5-dienone (104) generates a tertiary carbocation and loss of a proton forms the pentachlorocyclohexa-2,4-dienone (105) (Scheme 4.15).



If the Cl^+ ion is captured by the tetrachlorocyclohexa-2,4-dienone (100) a delocalised cation (107) would be generated, and further chlorine addition would give the cyclohex-3-enone (101) or the conjugated ketone (102) (Scheme 4.16).



Addition of chlorine to the dienone (100) in acetic anhydride proceeded rapidly compared with the reaction in acetic acid containing sodium acetate. After four hours no tetrachloro dienone (100) remained. This is consistent with the trend exhibited by the other chloro dienones discussed earlier. In previous cases even though the reactions in acetic anhydride were carried out at -10° , they were typically much faster than those in acetic acid/sodium acetate at 20° . For example, the chlorination of the mixture of trichloro dimethyl dienones (48) and (49) in acetic acid containing sodium acetate at 22° still contained 58% unreacted dienones (48) and (49) after six hours, whereas the reaction took less than two hours for completion in acetic anhydride at -10° .



The reasons for the increased rate of chlorine addition in acetic anhydride are not known. However, one possibility could be that an equilibrium exists between molecular chlorine/acetic anhydride and acetyl chloride/chlorine acetate, as shown over.



It is known that chlorine acetate is more reactive than molecular chlorine because the former can transfer positive chlorine to an olefin with greater efficiency than molecular chlorine.⁴⁸ If this is occurring however, the equilibrium does not favour the formation of chlorine acetate and acetyl chloride to any great extent, as the latter could not be detected in a solution of chlorine and acetic anhydride in deuteriochloroform by ¹³C n.m.r.

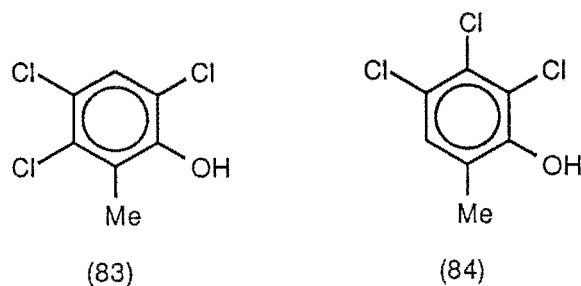
In summary, 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100) reacts slowly (14 days for complete reaction) with chlorine in acetic acid by 2,5-addition, but it is not clear if this is occurring by nucleophilic or electrophilic mechanisms. In acetic anhydride, electrophilic 2,5-addition is the favoured reaction pathway, forming the cyclohex-3-enone (101) in moderate yield (49%). The cyclohexa-2,5-dienones (104) and (105) (total yield 18%) are believed to form by rearrangements of the tetrachlorocyclohexa-2,4-dienone (100).

In contrast, 2,3-addition occurs rapidly (less than two hours) to 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85) by nucleophilic mechanisms. Blocking C3 of the dienone slows the reaction considerably.

CHAPTER FIVE

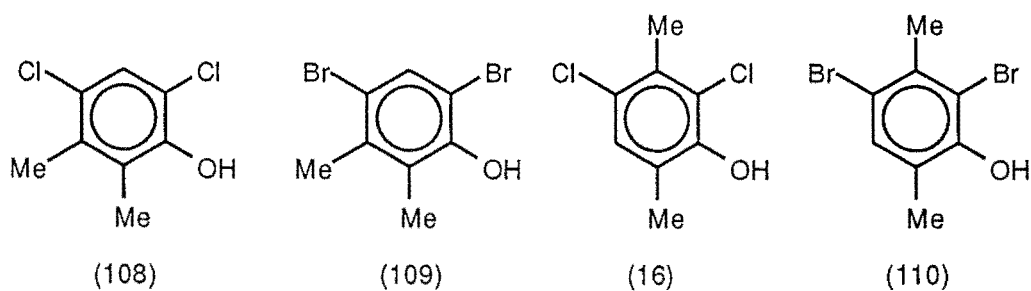
CHLORINATION OF THE DIHALO DIMETHYL PHENOLS

It was shown in Chapter Four that the trichloro methyl phenols (83) and (84) react by nucleophilic mechanisms in acetic acid, and if these pathways are suppressed the addition of chlorine by electrophilic mechanisms is very slow.



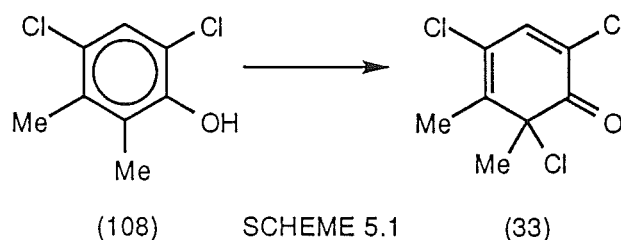
Replacing a chloro substituent with a methyl group should have a large effect on the reactivity due to the changes in the electron density and distribution on the aromatic ring. These changes were of interest as a comparison with other substituted phenol systems.

The reactions of four phenols, namely 2,4-dichloro-5,6-dimethylphenol (108) and the dibromo equivalent, 2,4-dibromo-5,6-dimethylphenol (109), 2,4-dichloro-3,6-dimethylphenol (16) and the equivalent dibromo compound, 2,4-dibromo-3,6-dimethylphenol (110) are discussed in this chapter.



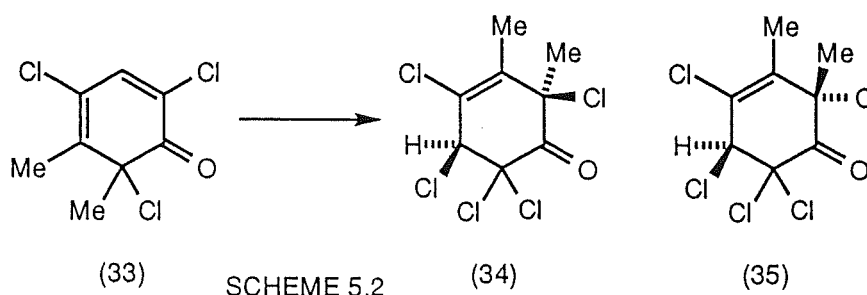
5.1 Chlorination Reactions of 2,4-Dichloro-5,6-dimethylphenol (108):

The formation of 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) (Scheme 5.1) was effected by addition of chlorine (1.2 mole equivalents) to a solution of the phenol (108) in carbon tetrachloride containing pyridine. As for the other substituted phenols, light was excluded from the flask to eliminate free radical side chain chlorination. (Detailed reaction conditions are set out in the experimental section relating to Chapter Five). This reaction gave essentially pure trichloro dienone (33), which was identical with authentic material. The structure of this compound had been assigned earlier on the basis of its spectroscopic data.¹⁸



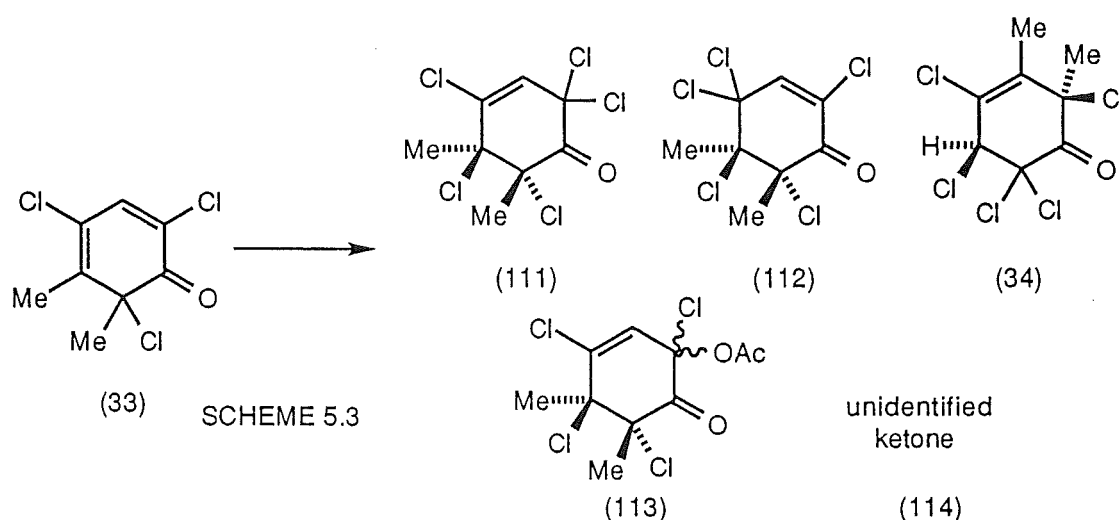
5.1.1 Reaction of Chlorine With 2,4,6-Trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) in Acetic Acid

Addition of chlorine to the trichloro dienone (33) was complete within two hours in the presence of a small amount of concentrated hydrochloric acid (0.05 mol l⁻¹). The reaction gave two products, as shown in Scheme 5.2. The *cis* compound (34) was the major isomer formed (72%). Both compounds were known, and their structures had been assigned earlier on the basis of their spectroscopic data.²⁵



5.1.2 Reaction of Chlorine With 2,4,6-Trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) in Acetic Acid Containing Sodium Acetate

Addition of sodium acetate to the reaction medium slowed the reaction considerably, such that the reaction time was extended to 24 hours for complete reaction. The reaction gave a mixture of five products (Scheme 5.3) which were separated by chromatography.



Eluted first was the 2,2-dichlorocyclohex-3-enone (111) (62%), and its structure was assigned on the basis of its spectroscopic data. The infrared spectrum (ν_{max} 1761, 1635) of compound (111) indicated a non-conjugated enone system, and the position of the olefinic proton in the ^1H n.m.r. spectrum (δ 6.503) supports the lack of conjugation. The C5/C6 stereochemistry was assigned after comparison with compound (115) (over). From the X-ray crystal structure (over) it can be seen that the C5-chlorine adopts the axial orientation, and both the C5-methyl group (C7) and the C6-methyl group (C8) adopt the equatorial orientation.²⁹ This positions both methyl groups well clear of deshielding by diaxial interactions with chloro substituents, which accounts for the upfield position of the methyl signals (δ 2.07, 2.02) in the ^1H n.m.r. spectrum of compound (115).

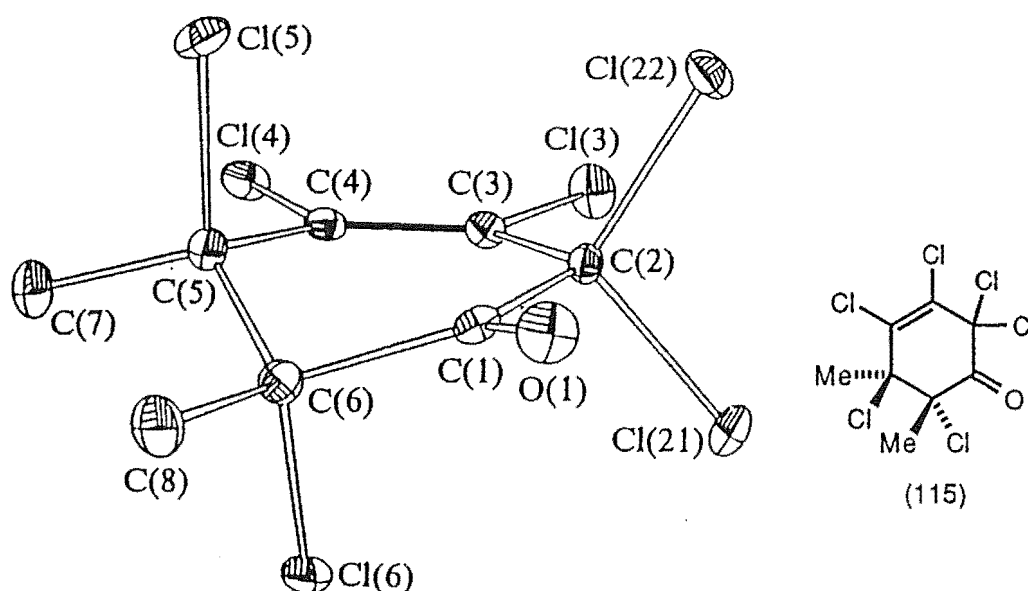


Figure 5.1 Perspective Drawing of Compound (115), Ellipsoids
are at 20% Probability Level

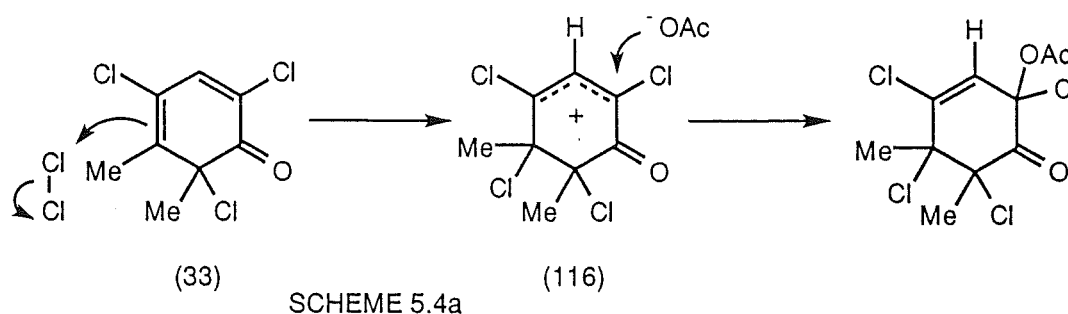
In comparison, the methyl signals of compound (111) (δ 2.008, 1.988) are similar, suggesting a common orientation of these two groups with those of compound (115). The slight downfield shift of resonances in compound (115) is due to the presence of the additional electron withdrawing chlorine atom at C3 in that structure relative to compound (111).

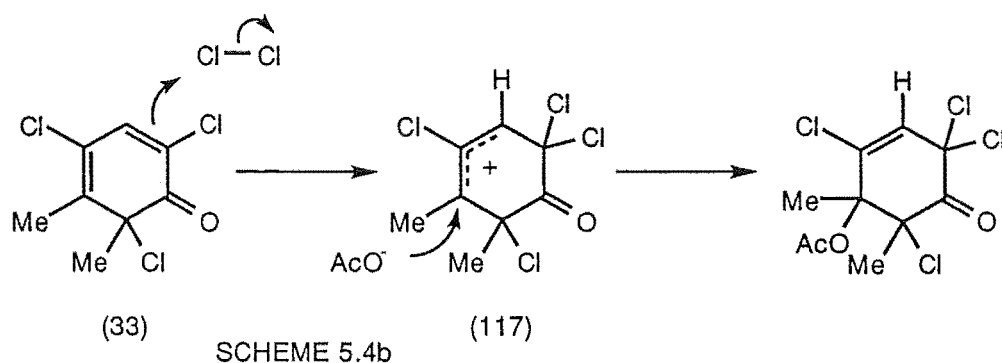
The second compound to be eluted was the conjugated ketone (112) (22%) and its structure was assigned on the basis of its spectroscopic data. Mass spectroscopy confirmed the molecular formula, and the presence of conjugation was established by the ultraviolet (λ_{max} 250 nm, ϵ 7450) and infrared (ν_{max} 1726, 1616) spectra, and was further supported by the downfield position of the olefinic proton in the ^1H n.m.r. spectrum (δ 7.074). As mentioned in Chapter One it is common for cyclohex-2-enones to exist in a flattened half chair conformation with the C5-chlorine in the equatorial position, and the other C5 substituent adopting the axial orientation. Making the assumption that compound (112) adopts a similar

conformation, the stereochemistry at C5/C6 can be assigned on the basis of the ^1H n.m.r. spectrum. If the C5-chlorine is equatorial, then the C5-methyl group is axial, and will be deshielded only by the *gauche* chlorine atoms at C4 and C6; this is reflected in the relatively upfield position of its ^1H n.m.r. signal (δ 2.044). The signal for the C6-methyl group is shifted downfield (δ 2.151) indicating that this group exists in the axial orientation where it is deshielded by the *pseudo*-axial C4-chloro substituent.

The third compound to be eluted was the cyclohex-3-enone (34) (3%), identical to authentic material (Section 5.1.1).

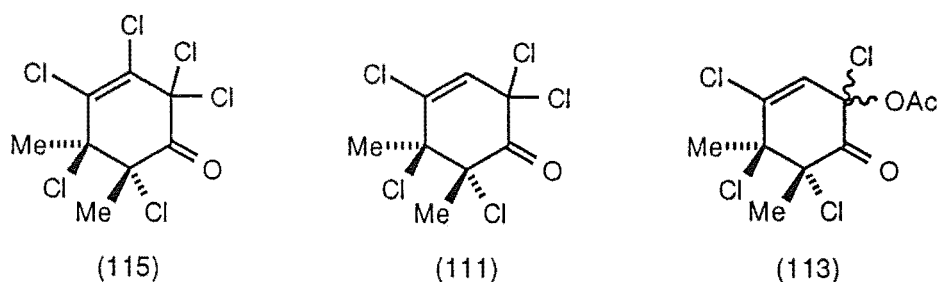
The next compound eluted was the acetate (113) (6%), and its structure was assigned tentatively from mechanistic considerations and on the basis of its spectroscopic data. The ^1H n.m.r. spectrum shows the downfield proton (δ 6.069) is attached to a non-conjugated olefinic carbon, i.e. C3. The third methyl group signal (δ 2.125, 2.110, 1.902) indicates the presence of an acetate group. Assuming compound (113) is formed by electrophilic addition, the initial chlorine attack can occur at either C2 or C5 of the trichloro dienone (33) (Scheme 5.4). The presence of the non-conjugated olefinic H3 in compound (113) necessitates subsequent attack by acetate ion at either C2 of the intermediate (116) (Scheme 5.4a), or at C5 of the intermediate (117) (Scheme 5.4b, over).





It has been observed that 2,4-dichloro delocalised cations such as the intermediate (116) (Scheme 5.4a) have a strong preference for nucleophilic attack at C2 (e.g. Section 3.7).

The intermediate in Scheme 5.4b, (117), requires attack of acetate ion exclusively at C5 to form the acetate product. Although the electron donating methyl group would stabilise the positive charge at C5 of the intermediate (117), making this site favourable for acetate ion attack, steric considerations should suggest that some acetate ion attack at the unsubstituted C3 site should also occur. However, as only one acetate (113) is formed experimentally it is assumed that the reaction does not proceed through the intermediate (117), but rather it proceeds as depicted in Scheme 5.4a. The stereochemistry at C5 and C6 was assigned after comparison with compounds (115) and (111).



The C5-chlorine of cyclohex-3-enones usually adopts the axial position, placing the other C5 substituent in the equatorial orientation. In the cyclohex-3-enones (111) and (115) the C5-methyl groups occupy the

equatorial position and the ^1H n.m.r. chemical shifts of these are δ 2.008 and δ 2.07 respectively. It is believed that the C5-methyl group of the acetoxy compound (113) also adopts the equatorial position because of the similar ^1H n.m.r. signal (δ 2.110).

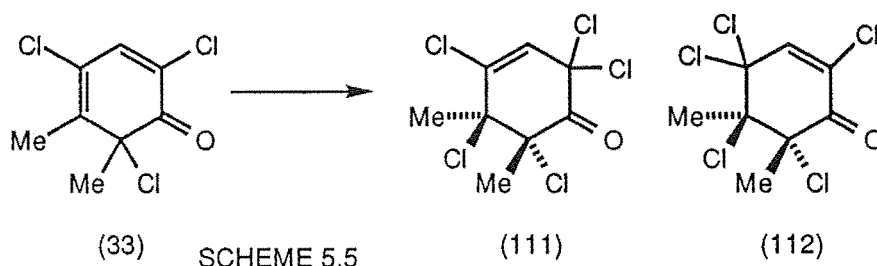
R. J. Martyn demonstrated that additional chlorine substituents on the ring tended to move the chemical shifts in the ^1H n.m.r spectrum downfield.²⁵ This trend is illustrated in compounds (111) and (115). The C6-methyl signal of (115) occurred at δ 2.02, and replacement of the C3-chlorine with a proton, as in compound (111) shifted the C6-methyl signal upfield to δ 1.988. Subsequent replacement of a C2-chlorine with a less electron withdrawing acetate group should shift the C6-methyl signal further upfield. This is observed in compound (113) where the C6-methyl signal occurred at δ 1.902.

The stereochemistry at C2 cannot be assigned from the spectroscopic data. However on the basis of the preferred stereochemistry of other acetoxy compounds, the acetate function is likely to be *cis* to the C5 chlorine.

The last compound to be eluted was a hydroxy ketone (114) (7%) which was isolated only in an impure state. The structure of this compound remains unknown.

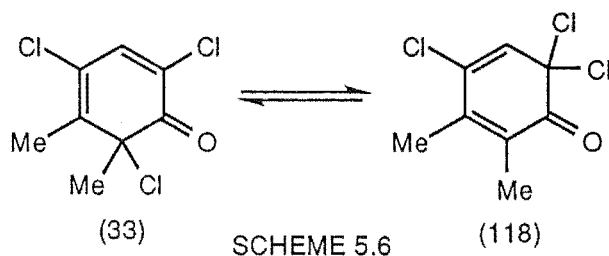
5.1.3 Reaction of Chlorine With 2,4,6-Trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) in Acetic Anhydride

Addition of chlorine to the trichloro dienone (33) was complete in two hours and gave the cyclohex-3-enone (111) (70%) and the conjugated ketone (112) (30%) (Scheme 5.5, over). Both were identified by comparison with authentic material (Section 5.1.2).



5.1.4 Semi-Empirical Calculations of a Possible Dienone Interconversion

Only the 2,4,6-trichloro dienone (33) was observed experimentally, no 4,6,6-trichloro dienone (118) was seen (Scheme 5.6). However, the energetics of this interconversion were investigated as a comparison with the interconversion of other dienone systems studied.



The AM1 parameter set was used in the program MOPAC to calculate the heats of formation of the two trichloro dienones (33) and (118). These were found to be (33) $-122.2 \text{ kJ mol}^{-1}$ and (118) $-116.3 \text{ kJ mol}^{-1}$. Application of a Boltzmann distribution gives a predicted ratio of (33) : (118) of 92 : 8 at 22° . This ratio is closer to the experimentally observed ratio of 100 : 0 than calculated for other 2-chloro-6-methyl dienones mentioned in earlier Chapters, and is compared with those results in Appendix Two.

The heat of formation of the transition state was also calculated. An appropriate transition state structure was determined and refined using the gradient minimisation procedure in MOPAC. Vibrational analysis revealed a single negative eigenvalue, indicating that the structure represents a saddle point on the potential energy surface. The geometry of the transition state is presented over (Figure 5.2).

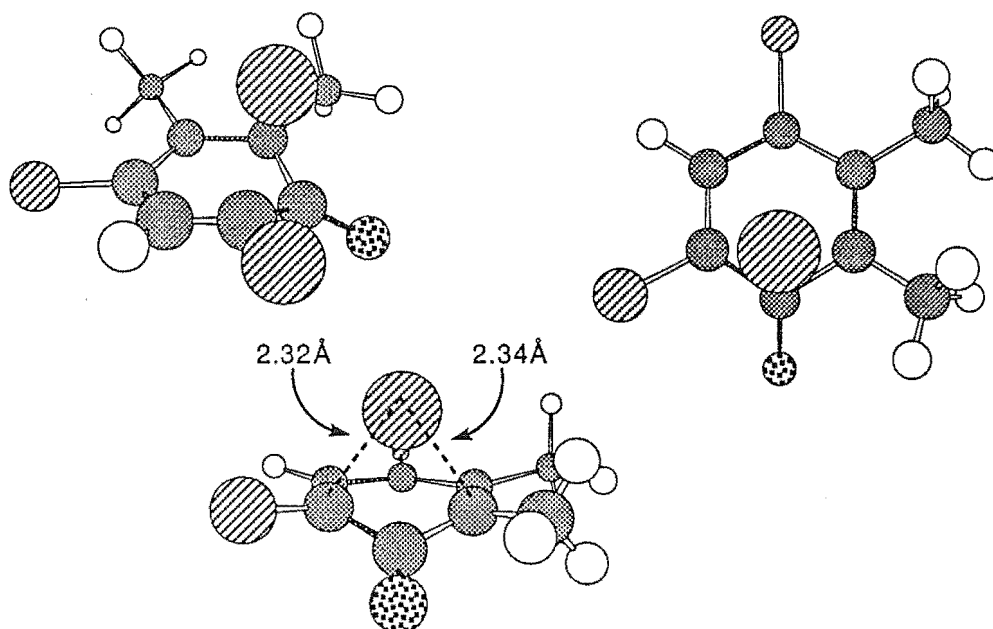


Figure 5.2 AM1 Calculated Geometry of the Transition State in the Interconversion of the Trichloro Dienones (33) and (118).

The heat of formation was calculated as being 44.9 kJ mol^{-1} . This gives a barrier to interconversion of the 2,4,6-trichloro dienone (33) to the 4,6,6-trichloro dienone (118) of $167.1 \text{ kJ mol}^{-1}$, a value similar to the barriers of other dienone interconversions mentioned earlier.

A potential energy hypersurface was calculated for this interconversion, for C2-chlorine and C6-chlorine distances ranging from 1.5 \AA to 3.6 \AA , and is presented in Figure 5.3 (over). As was seen in the other two hypersurfaces (Section 4.1.4, 2.4) the transition state 'saddle' and the dienone 'valleys' can be clearly seen.

The PM3 parameter set was also used to calculate the heats of formation of the two trichloro dienones (33) and (118) and of the transition state between them. The values calculated were, for the 2,4,6-trichloro dienone (33) $-155.6 \text{ kJ mol}^{-1}$, for the 4,6,6-trichloro dienone (118) $-157.7 \text{ kJ mol}^{-1}$ and for the transition state $-14.3 \text{ kJ mol}^{-1}$. These figures correspond to a Boltzmann

distribution of (33) : (118) of 30 : 70 at 22°, and a barrier to the conversion of (33) to (118) of 141.3 kJ mol⁻¹ (See Appendix Two).

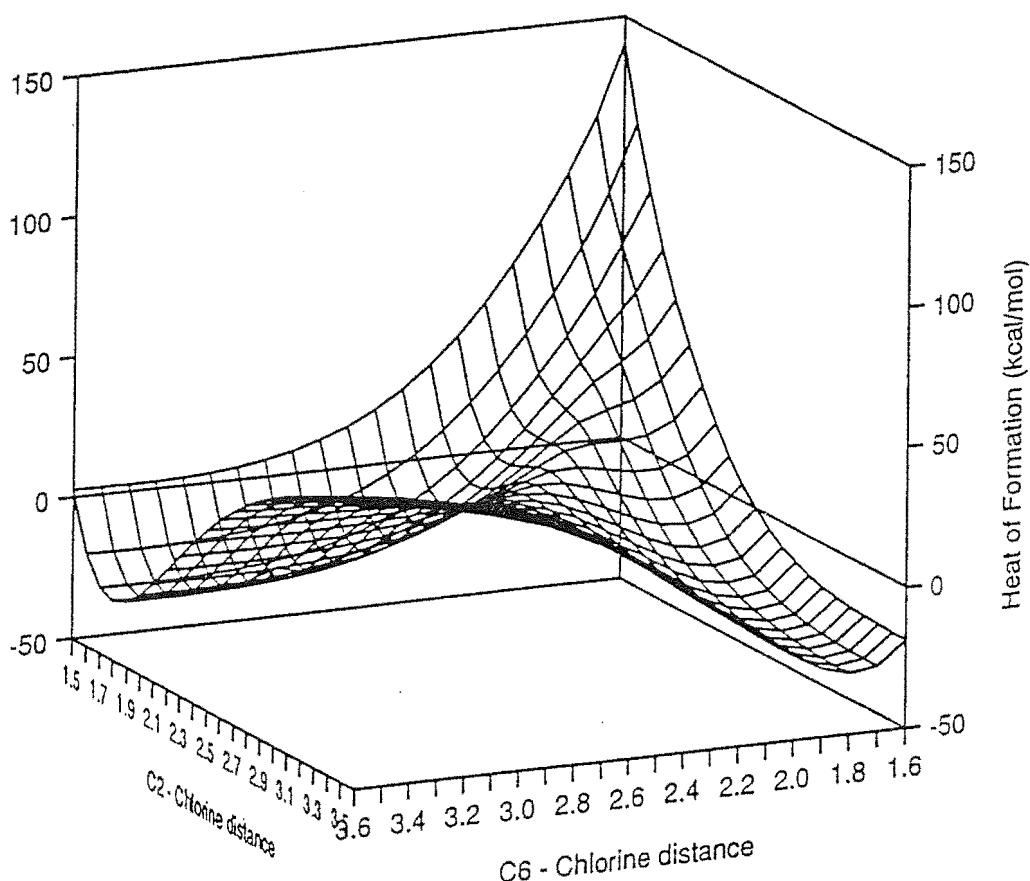


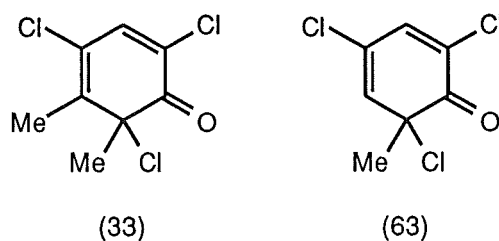
Figure 5.3 AM1 Calculated Potential Energy Hypersurface

The energy of the barrier is similar to those found for other dienones, but the PM3 method fails to predict the ratio of the two trichloro dienones accurately. Calculations with this parameter set indicate the 4,6,6-trichloro dienone (118) to be present as 70% of a mixture of trichloro dienones, whereas this compound is not observed experimentally.

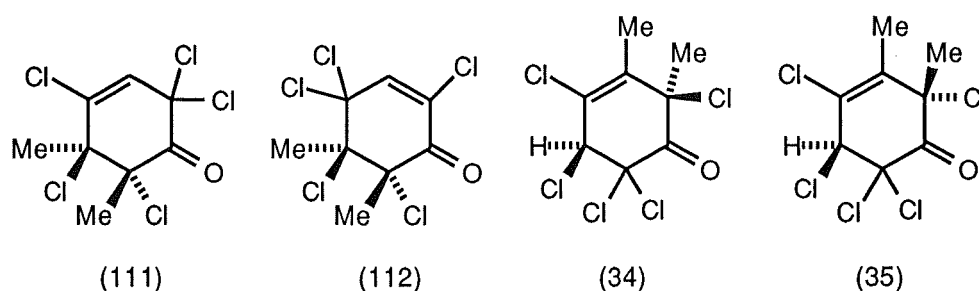
It is believed that the interconversion of (33) and (118) is not occurring, and that the reactions discussed in this section proceed from the 2,4,6-trichloro dienone (33).

5.1.5 Solvent Effect Study

As discussed in Section 3.6, due to large variations in yields of the products on changing solvent a study, identical to that carried out with 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (63), was undertaken using 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) (See experimental section relating to Chapter Five).

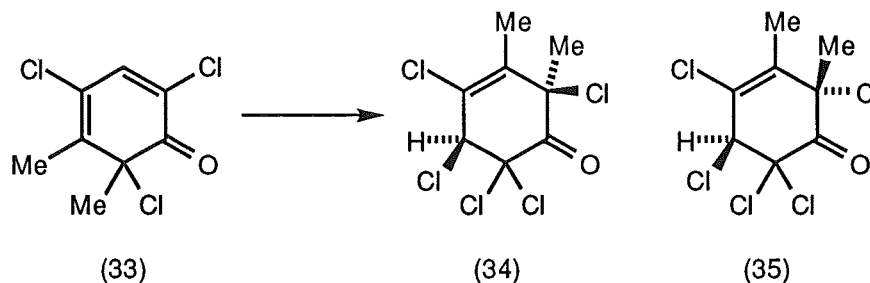


At high levels of acetic anhydride the reaction gave mostly the electrophilic addition products (111) and (112) in addition to a small amount of the electrophilic addition products (34) and (35). Only at very low levels of acetic anhydride did the yields of the nucleophilic products increase. These results may be accounted for on the assumption that the nucleophilic addition of chlorine requires chloride ion, and it has been demonstrated that acetic anhydride can effectively consume this.²⁶ At very low acetic anhydride levels trapping of chloride ion is incomplete and the more favoured nucleophilic addition becomes predominant.

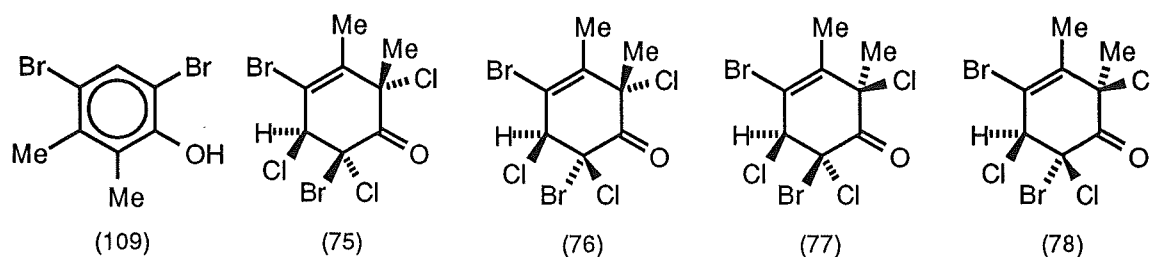


5.2 Reactions of 2,4-Dibromo-5,6-dimethylphenol (109):

The *gem*-dichloro moiety of the cyclohex-3-enones (34) and (35) obscures stereochemical information about the addition of chlorine to the trichloro dienone (33) in acetic acid.

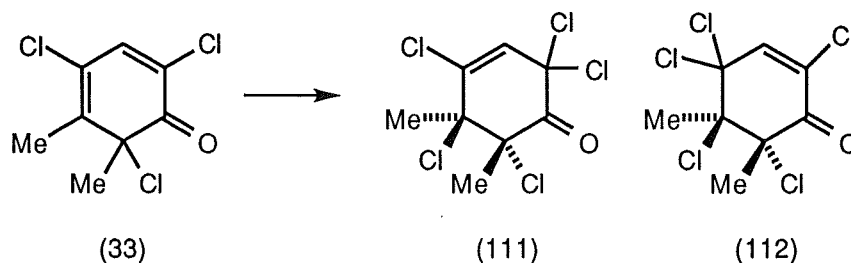


However, R. J. Martyn demonstrated that 2,4-dibromo-5,6-dimethylphenol (109) reacts with chlorine in acetic acid by nucleophilic 2,3-addition to give the four products shown below.²⁵

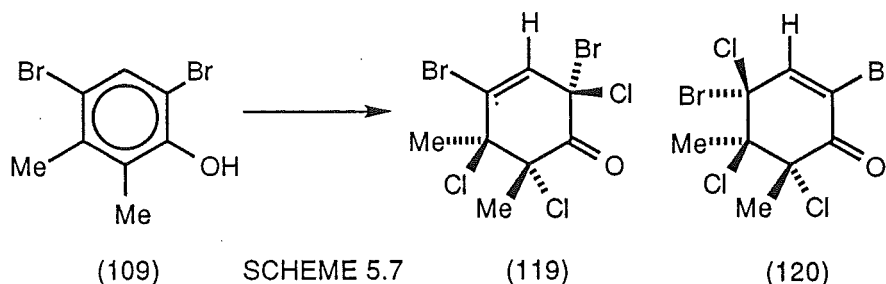


The presence of all four stereoisomers indicates that the nucleophilic 2,3-addition products (34) and (35) occur by *cis* and *trans* addition of chlorine.

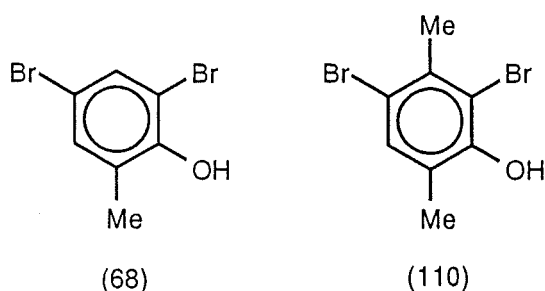
The formation of compounds (111) and (112) occurs by electrophilic 2,5- and 4,5-addition respectively. However, the stereochemistry of these additions are also obscured by the presence of the *gem*-2,2-dichloro moiety in the cyclohex-3-enone (111) and the *gem*-4,4-dichloro moiety in the conjugated ketone (112).



For this reason the products of electrophilic addition of chlorine to 2,4-dibromo-5,6-dimethylphenol (109) were of interest. Reaction of the phenol (109) with chlorine in acetic anhydride proceeded rapidly giving two products (Scheme 5.7).

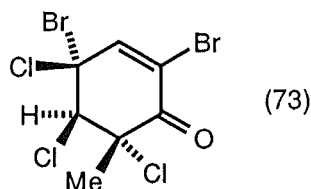


The first compound to be eluted from a silica gel Chromatotron plate was the cyclohex-3-enone (119) (70%), and its structure was assigned on the basis of its spectroscopic data. The infrared spectrum (ν_{\max} 1755, 1622) indicated a non-conjugated enone, and this was supported by the upfield position of the olefinic proton (δ 6.858) in the ^1H n.m.r. spectrum. The close similarity of the chemical shifts of the methyl groups (δ 2.016 and δ 2.011) with those of the cyclohex-3-enone (111) (δ 2.008, 1.988) indicate that the methyl groups in these two compounds share a common orientation, i.e. in the cyclohex-3-enone (119) the methyl groups both occupy equatorial positions and hence are *trans*. Without the C2-epimer of compound (119) for comparison, the stereochemistry at C2 cannot be assigned from the spectroscopic data. However, from the reactions of 2,4-dibromo-6-methylphenol (68) (Section 3.5) and 2,4-dibromo-3,6-dimethylphenol (110) (Section 5.5) in acetic anhydride it is known that electrophilic 2,5-addition occurs in a *cis* manner.



As only one cyclohex-3-enone was formed in this reaction, and the reaction was carried out in acetic anhydride which is known to trap free chloride ion, the migration of which to the reverse side of the substrate molecule is necessary for *trans* addition, it is likely that the chlorine at C2 is *cis* to the chlorine at C5. Unfortunately, compound (119) could not be induced to crystallise and a definitive structure determination by X-ray crystallography was not possible.

The second compound to be eluted was the conjugated ketone (120) (30%) and its structure was assigned on the basis of its spectroscopic data. The infrared (ν_{\max} 1722, 1605) and ultraviolet (λ_{\max} 276 nm, ϵ 3680) spectra indicate the conjugation of the unsaturated ketone system. This is supported by the downfield position of the olefinic proton (δ 7.506) in the ^1H n.m.r. spectrum. The similarities of the chemical shifts of the methyl groups in the ^1H n.m.r. spectrum (δ 2.188, 2.081) with those of the conjugated ketone (112) (δ 2.151, 2.044) indicate that a common orientation exists between the C5 and C6 methyl groups in these two compounds, i.e. both methyl groups are axial, with the C5 and C6-chlorine substituents equatorial. Compound (120) also could not be crystallised and, in the absence of an X-ray crystal structure, the *cis*-4,5-dichloro stereochemistry is tentatively assigned on the same mechanistic basis as for compound (119) (above), and for compound (73), the *cis*-4,5-dichloro conjugated ketone formed in the reaction of 2,4-dibromo-6-methylphenol (68) in acetic anhydride (Section 3.5)



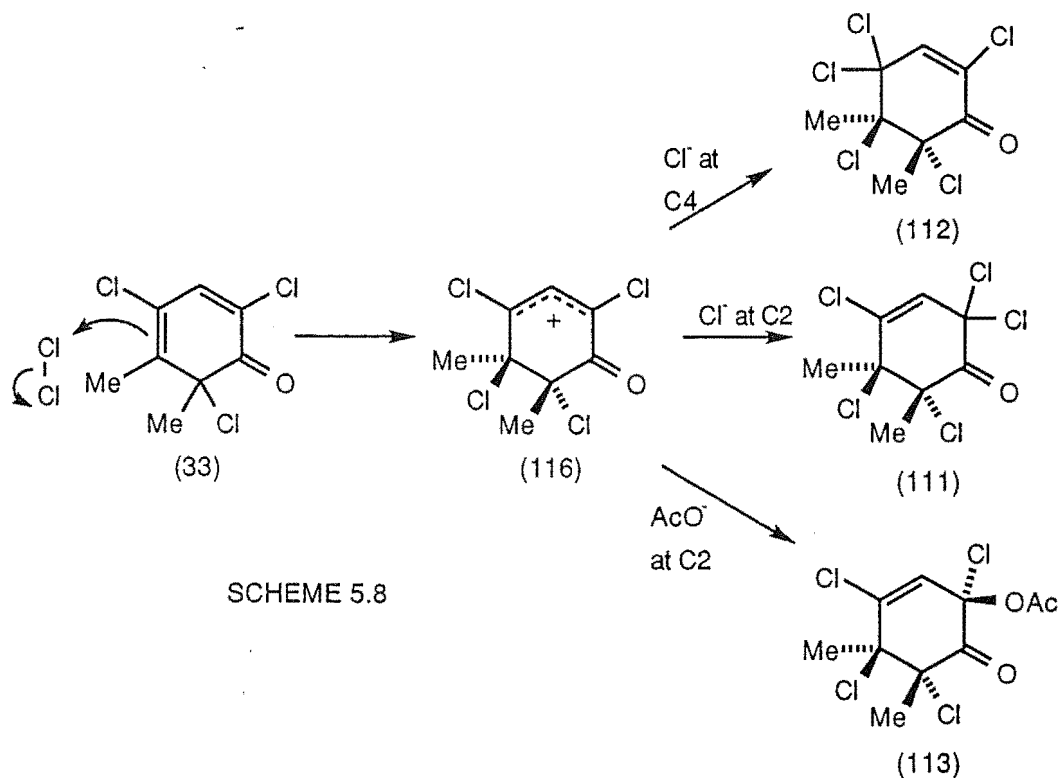
5.3 Discussion:

(a) In Acetic Acid

The reaction of chlorine with the trichloro dienone (33) proceeds rapidly in acetic acid by nucleophilic 2,3-addition. From comparison with the reactions of 2,4-dibromo-5,6-dimethylphenol (109) with chlorine in acetic acid by Martyn²⁵ it is believed that the nucleophilic 2,3-addition of chlorine to the trichloro dienone (33) occurs non-stereospecifically.

(b) In Acetic Acid/Sodium Acetate

This reaction proceeds to completion within 24 hours giving the electrophilic 2,5-addition product (111) as the major component of the mixture (62%). It is believed that both this compound and the conjugated ketone (112) form by initial attack of chlorine at C5 of the trichloro dienone (33) *trans* to the C6-chloro substituent, to generate the delocalised cationic intermediate (116) (Scheme 5.8).



Attack on the intermediate (116) by chloride ion can occur at C2 or at C4 to form the cyclohex-3-enone (111) and the conjugated ketone (112) respectively, or by acetate ion at C2 to give the acetoxy compound (113). It is believed that the small amount (3%) of the 2,3-addition product (34) forms by incomplete suppression of nucleophilic addition, as this compound is not formed in the reaction in acetic anhydride, which is more effective at blocking nucleophilic addition.

(c) In Acetic Anhydride

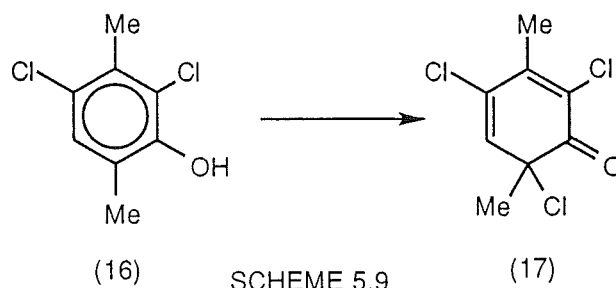
The reaction of chlorine with the trichloro dienone (33) occurred rapidly taking less than two hours for complete reaction to give the cyclohex-3-enone (111) and the conjugated ketone (112). The absence of added acetate ion in solution accounts for the lack of the acetoxy compound (113) formed in the acetic acid/sodium acetate reaction. Both products (111) and (112) presumably form by initial chlorine attack at C5 of the trichloro dienone (33), as depicted in Scheme 5.8 (above). It is believed that electrophilic 2,5- and 4,5-addition of chlorine both occur in a *cis* fashion as acetic anhydride traps free chloride ion, the migration of which is required to the reverse face of the substrate molecule for *trans* addition. Further support of this was sought from the reaction of the dibromo dimethyl phenol with chlorine in acetic anhydride. Unfortunately both products from this reaction, the conjugated ketone (120) and the cyclohex-3-enone (119), were not crystalline, and thus conclusive evidence of the stereochemistry of the chlorine addition by X-ray crystal analysis was not possible.

In summary, the 2,4-dihalo-5,6-dimethylphenols react with chlorine in acetic acid by nucleophilic 2,3-addition in a non-stereospecific manner. However, there is some preference for attack of chloride ion at C3 in the trichloro dienone (33) to occur *cis* to the C6-chloro substituent. The electrophilic reactions are not appreciably slower with 2,5-addition being the

favoured mode of reaction, forming the cyclohex-3-enone (111) (70%), with 4,5-addition occurring to a lesser extent to form the conjugated ketone (112) (30%).

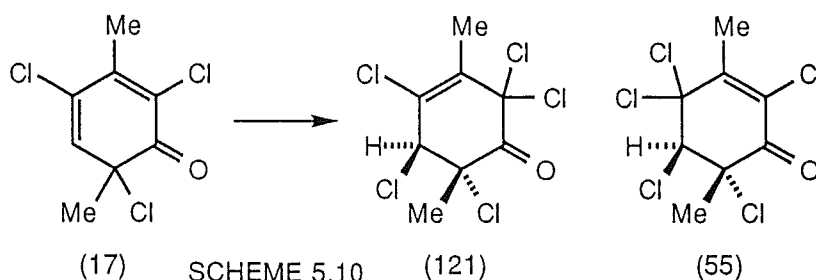
5.4 Chlorination Reactions of 2,4-Dichloro-3,6-dimethylphenol (16):

The 2,4,6-trichloro dienone (17) was prepared in the usual manner, and gave essentially pure dienone (17) (Scheme 5.9), which was identical with authentic material.^{18,25}



5.2.1 Reaction of Chlorine with 2,4,6-Trichloro-3,6-dimethylcyclohexa-2,4-dienone (17) in Acetic Acid

Chlorine addition to the trichloro dienone (17) gave after six hours two products, the cyclohex-3-enone (121) (69%) and the conjugated ketone (55) (31%) (Scheme 5.10). Both compounds were identical with authentic material, and their structures had been assigned earlier on the basis of their spectroscopic data.^{18,25}



The structure of compound (121) was confirmed by single crystal X-ray analysis. A perspective drawing of *trans*-2,2,4,5,6-pentachloro-3,6-dimethylcyclohex-3-enone, m.p. 130-132°, $C_8H_7Cl_5O$ is presented in Figure 5.4 with corresponding atomic coordinates in Table 6.8.

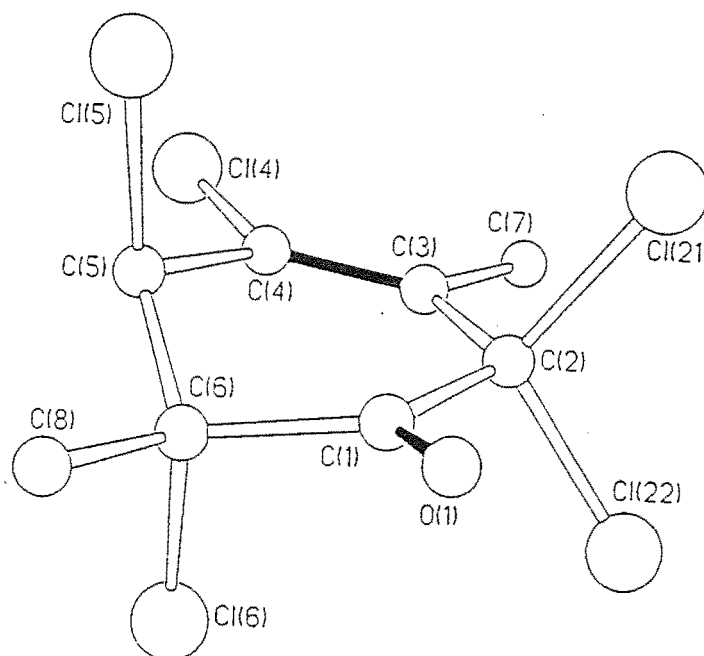


Figure 5.4 Perspective Drawing of Compound (121)

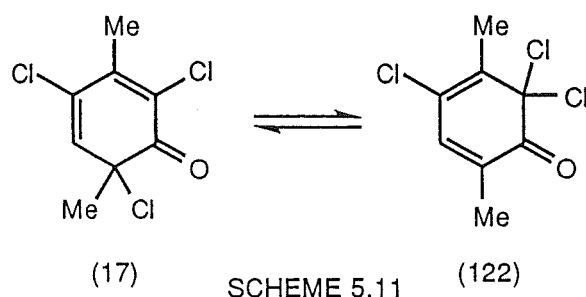
In the solid state the alicyclic ring of compound (121) exists in a flattened skew-boat conformation [torsion angles C(1)-C(2)-C(3)-C(4) 10.3°; C(3)-C(4)-C(5)-C(6) -29.8°; C(3)-C(4)-C(5)-Cl(5) 90.1°] similar to analogous structures reported earlier.²⁹

5.4.2 Reaction of Chlorine with 2,4,6-Trichloro-3,6-dimethylcyclohexa-2,4-dienone (17) in Acetic Anhydride

Chlorination of the trichloro dienone (17) occurred rapidly (2 h.) to give the same products as the reaction in acetic acid, namely the cyclohex-3-enone (121) (85%) and the conjugated ketone (55) (15%). Both of these were identical with authentic material.^{18,25}

5.4.2 Semi-Empirical Calculations of a Possible Dienone Interconversion

Although only the 2,4,6-trichloro dienone (17) was observed the possibility existed that the chlorine addition reactions proceeded through the 4,6,6-trichloro dienone (122) (Scheme 5.11). The energetics of this system were investigated by semi-empirical calculations.



The heats of formation of the two dienones (17) and (122) were calculated using the AM1 parameter set in the program MOPAC. These were found to be (17) $-121.8 \text{ kJ mol}^{-1}$ and (122) $-119.1 \text{ kJ mol}^{-1}$. Application of a Boltzmann distribution gives a predicted ratio of (17) : (122) of 75 : 25 at 22° (the experimentally observed ratio was 100 : 0).

The heat of formation of the transition state was also calculated. An appropriate transition state was determined and refined using the gradient minimisation procedure in MOPAC. Vibrational analysis revealed a single negative eigenvalue, indicating that the structure represents a saddle point on the potential energy surface. The geometry of the transition state is presented in Figure 5.5 (over). The migrating chlorine atom is almost symmetrically displaced between C2 and C6.

The heat of formation was calculated to be 45.8 kJ mol^{-1} , giving a barrier to the conversion of (17) to (122) of $167.6 \text{ kJ mol}^{-1}$. This value is similar with the values found for other 2-chloro-6-methyl dienones (See Appendix 2).

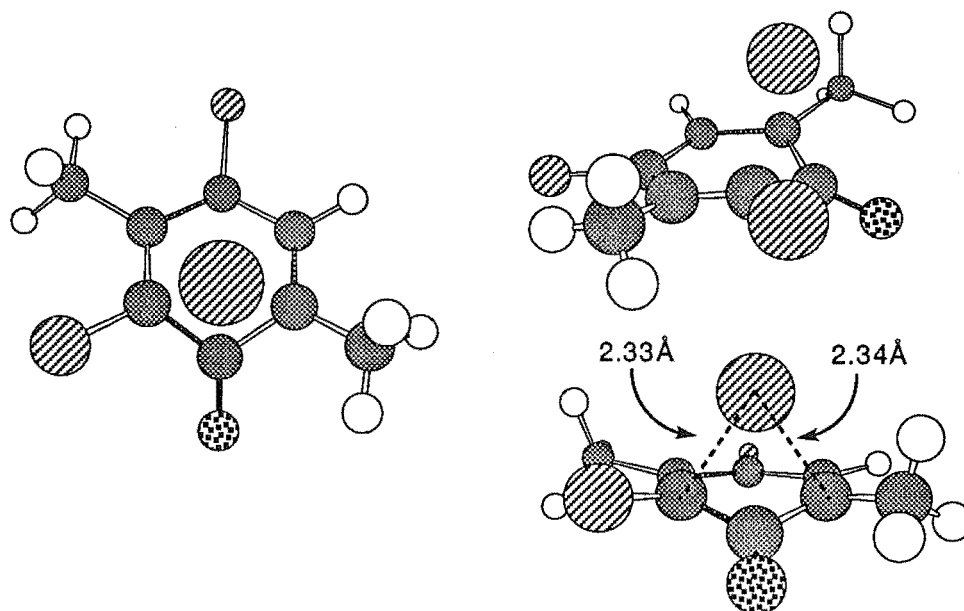


Figure 5.5 AM1 Calculated Geometry of the Transition State in the Interconversion of the Dienones (17) and (122)

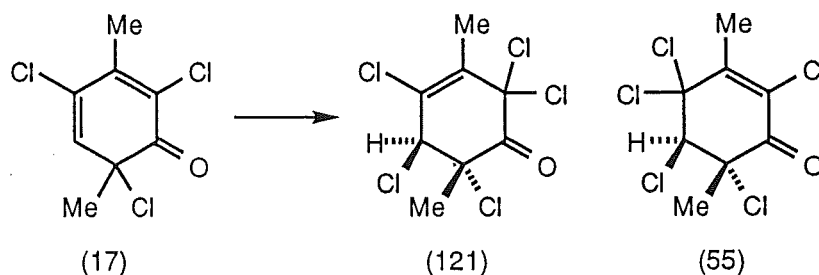
The heats of formation of the two trichloro dienones (17) and (122) and the transition state between them was calculated using the PM3 parameter set in the program MOPAC. The energies were found to be, for the 2,4,6-trichloro dienone (17) $-159.9 \text{ kJ mol}^{-1}$, for the 4,6,6-trichloro dienone (122) $-157.9 \text{ kJ mol}^{-1}$, and for the transition state $-16.7 \text{ kJ mol}^{-1}$. This corresponds to a barrier to the conversion of (17) to (122) of $143.2 \text{ kJ mol}^{-1}$, and a predicted Boltzmann ratio of (17) : (122) of 30 : 70 at 22° . As the experimentally observed value is 100 : 0 it is clear the PM3 parameter set is not modelling this system accurately.

It has been assumed that the [1,5]-sigmatropic shift is not an important feature of the reactions of the 2,4,6-trichloro dienone (17) and that the chlorine addition reactions proceed directly from this dienone.

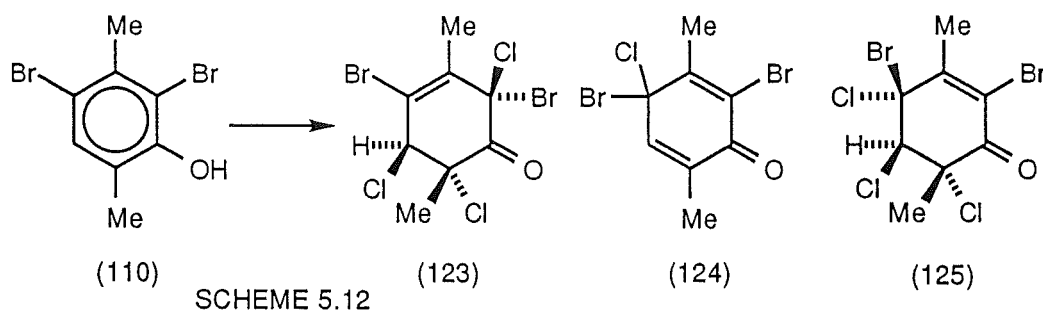
5.5 Reactions of 2,4-Dibromo-3,6-dimethylphenol (110):

The *gem*-dichloro moiety of compounds (121) and (55) formed in the reaction of chlorine with the 2,4,6-trichloro dienone (17) in acetic acid and

acetic anhydride obscures the stereochemistry of the addition of chlorine to these compounds.



For the above reason the reaction of chlorine with the dibromo phenol (110) was of interest. Chlorination of the phenol (110) in acetic anhydride gave a mixture of at least eight compounds. Several of these proved to be unstable on silica gel Chromatotron plates and on silica and cyanopropyl HPLC columns and could not be isolated. The remainder (*ca.* 70%) was separated on a silica gel / polyethylene glycol Chromatotron plate and were identified as being the compounds shown below (Scheme 5.12).



The first compound to be eluted was the cyclohex-3-enone (123) (56%), and its structure was determined by single crystal X-ray analysis. A perspective drawing of *r*-2,4-dibromo-2,*t*-5,*c*-6-trichloro-3,6-dimethylcyclohex-3-enone, $C_8H_7Br_2Cl_3O$, m.p. 123-125° is presented in Figure 5.6 (over), with corresponding atomic coordinates in Table 6.9. In the solid state the alicyclic ring exists in the skew-boat conformation [torsion angles C(1)-C(2)-C(3)-C(4) 12.3°; C(3)-C(4)-C(5)-C(6) -29.4°; C(3)-C(4)-C(5)-C(6) 92.3°], similar to other

cyclohex-3-enones.²⁹ The spectroscopic data are in accord with the established structure.

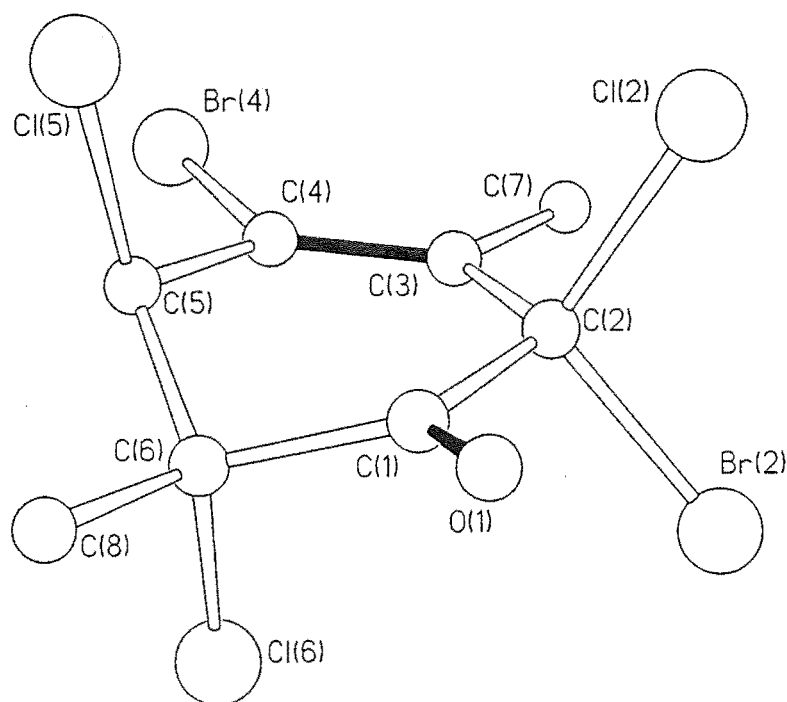


Figure 5.6 Perspective Drawing of Compound (123)

The next compound to be eluted was the cyclohexa-2,5-dienone (124) (6%), and its structure assigned on the basis of its spectroscopic data. An accurate mass could not be determined by mass spectroscopy. The infrared (ν_{\max} 1661, 1605) and ultraviolet (λ_{\max} 283, 254nm; ϵ 1370, 7250) spectra and the position of the C1 signal in the ^{13}C n.m.r. spectrum (δ 177.01) indicate the presence of a cross conjugated dienone. The ^{13}C n.m.r. spectra also showed four signals in the olefinic region (δ 155.80, 141.72, 130.28, 125.91) and only one signal corresponding to a sp^3 carbon bearing one or more halogen substituents (δ 77.21), supporting a cyclohexadienone structure. The ^1H n.m.r. spectrum showed the presence of allylic coupling between the olefinic proton (δ 6.970) and the upfield methyl (6-Me) signal (δ 2.015) with a coupling constant $J=1.6\text{Hz}$. The other methyl group (3-Me) gave a signal at δ 2.487, the downfield position of this being consistent with attachment to the β carbon of an α,β -unsaturated ketone.

The third compound to be eluted was the conjugated ketone (125) (8%), and its structure was determined by single crystal X-ray analysis. A perspective drawing of 2,*r*-4-dibromo-4,*c*-5,*t*-6-trichloro-3,6-dimethylcyclohex-2-enone, $C_8H_7Br_2Cl_3O$, m.p. 105-107° is presented in Figure 5.7, with corresponding atomic coordinates in Table 6.10. In the solid state the alicyclic ring exists in a flattened half-chair conformation with the C5-chlorine in the equatorial position, as is usual for cyclohex-2-enones [torsion angles C(2)-C(3)-C(4)-C(5) -19.2°; C(6)-C(1)-C(2)-C(3) -5.0°; Cl(5)-C(5)-C(6)-C(1) -178.4°]. The spectroscopic data are in accord with the established structure.

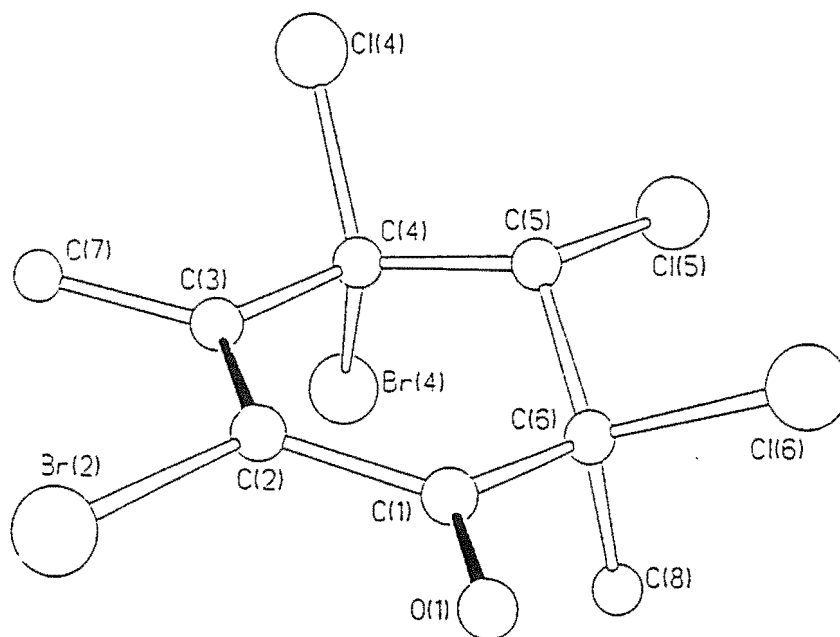
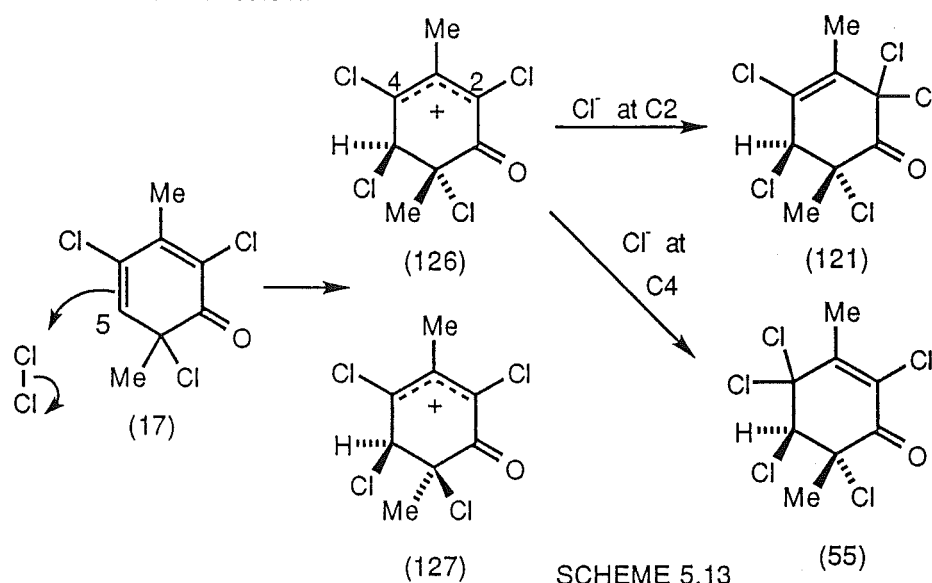


Figure 5.7 Perspective Drawing of Compound (125)

5.6 Discussion:

Chlorine addition to the trichloro dienone (17) in acetic acid gave two products, the conjugated ketone (55) and the cyclohex-3-enone (121). These form by 4,5-addition and 2,5-addition of chlorine respectively. The *gem*-dichloro moieties in each of these compounds obscures the stereochemistry of the addition, but the *trans*-C5/C6 chlorine arrangement is still formed. The reaction took six hours for complete consumption of the trichloro

dienone (17) to occur. It is believed that this reaction is occurring by electrophilic pathways because of the exclusively *trans*-C5/C6 chlorine stereochemistry. The first step of electrophilic 2,5-addition involves the addition of a chlorine atom to the trichloro dienone (17). As this is an endothermic process the transition state will occur late in the reaction coordinate, and thus, its structure will closely resemble the delocalised cation intermediate. This means that C5-chlorine bond formation will be nearly complete in the transition state, and interaction with the dipole of the C6-chlorine bond must be considered. A *cis*-5,6-dichloro arrangement, as in the intermediate (127) (Scheme 5.13), is unfavourable as the dipoles of the C5-chlorine bond and C6-chlorine bond exist in a *gauche* configuration. However, if the incoming chlorine attacks C5 of the dienone (17) from the opposite face to the C6-chlorine, the dipoles of the C5-chlorine and C6-chlorine bonds exist in an *anti* configuration in the transition state and the intermediate (126). This arrangement is lower in energy, and hence, is the preferred mode of reaction.



SCHEME 5.13

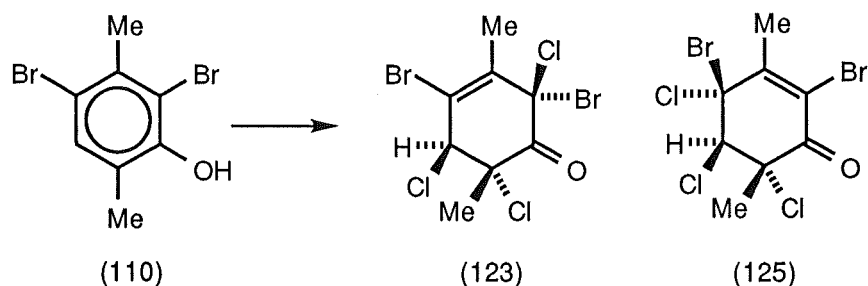
Semi-empirical calculations of the two possible intermediates (126) and (127) using the AM1 parameter set in the program MOPAC support the favoured

stability of the *trans*-5,6-chloro arrangement [(126) = 667.6 kJ mol⁻¹] over the *cis* arrangement [(127) = 681.9 kJ mol⁻¹].

The reaction in acetic anhydride was complete in two hours at -10°, giving the same products as the reaction in acetic acid, the conjugated ketone (55) and the cyclohex-3-enone (121). Both form through the delocalised cation (126), as shown in Scheme 5.13 (above).

The stereochemistry of the above reactions is obscured by the presence of the *gem*-dichloro moieties present in the products. Chlorination of 2,4-dibromo-3,6-dimethylphenol (110) in acetic anhydride sought to resolve this problem.

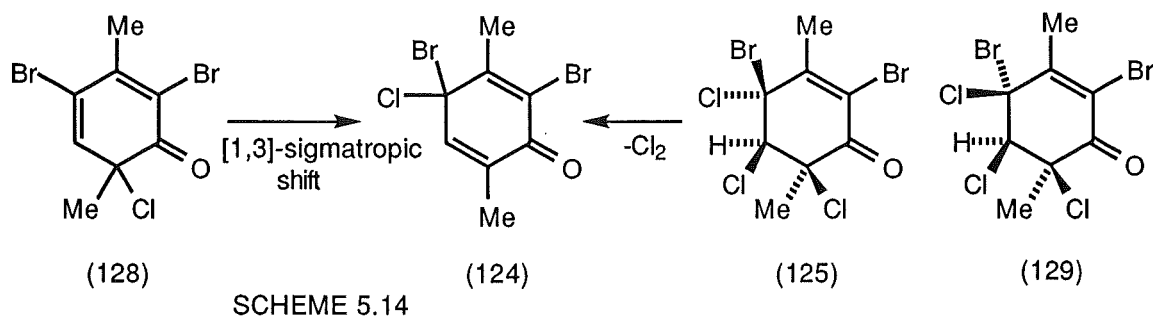
The reaction proved to be somewhat messy, with only *c.* 70% of the total products sufficiently stable for their isolation and characterisation. The major product isolated was the cyclohex-3-enone (123) (56%). The addition of chlorine across C2/C5 occurred in a *cis* fashion, as was expected for this solvent. However, the *trans* arrangement of chloro substituents across C4/C5 of the conjugated ketone (125) is unusual.



The formation of the *trans*-4,5-dichloro moiety of compound (125) requires migration of chloride ion to the reverse face of the substrate. It is somewhat surprising that this is occurring, as acetic anhydride is known to consume chloride ion.²⁶ However, compound (125) was present in low yield only

(8%) and as only 70% of the mixture was isolated and characterised, the possibility exists that the *cis*-4,5-dichloro compound may be a significant component of the remaining unidentified 30%.

The cyclohexa-2,5-dienone (124) is present only as a minor component of the mixture (6%). Although 4,4-dichlorocyclohexa-2,5-dienones are not formed spontaneously from 4,6-dichlorocyclohexa-2,4-dienones, documentation of the behaviour of bromochlorocyclohexadienones in this respect is scarce. For this reason the mode of formation of compound (124) is uncertain. It may be formed by a [1,3]-sigmatropic rearrangement of the 2,4-dibromo-6-chlorocyclohexa-2,4-dienone (128) or by loss of Cl₂ from C5/C6 of the conjugated ketone (125) or its C4-epimer (129) (Scheme 5.15).



The possibility that loss of Cl₂ was occurring from the conjugated ketone (125) was excluded by the observation that this compound was stable under the reaction conditions. As the conjugated ketone (129) and the cyclohexa-2,4-dienone (128) could not be isolated, the possibility of formation of the cyclohexa-2,5-dienone (124) from these compounds cannot be excluded.

In summary 2,4-dichloro-5,6-dimethylphenol (108) reacts with chlorine by nucleophilic mechanisms in acetic acid, to give 2,3-addition products. This is in contrast to the 2,4-dichloro-3,6-dimethylphenol (16) which reacts by electrophilic mechanisms. This difference is believed to arise because nucleophilic attack at C3 of the 3,6-dimethyl dienone (17) is disfavoured as

this attack occurs *ipso* to a methyl group. As well as the steric considerations, this site will be electron rich due to the electron donating property of the C3-methyl group, and thus unattractive for nucleophilic attack.

CHAPTER SIX

EXPERIMENTAL, APPENDICES AND REFERENCES

6.1 APPARATUS, MATERIALS AND INSTRUMENTATION

Infrared spectra were recorded on a Perkin-Elmer Series 1600 FTIR for liquid films and KBr disks. Ultraviolet absorption spectra were obtained using either Varian DMS-100 or a Perkin-Elmer Lambda-2 spectrophotometers with hexane or cyclohexane as solvent. Melting points were determined in open tubes and are uncorrected. ^1H and ^{13}C n.m.r. and nuclear Overhauser enhancement experiments were obtained for deuterio-chloroform solutions using TMS as an internal standard on either a Varian XL-300 or Unity 300 spectrometer. All chemical shifts are expressed as parts per million (ppm) downfield from TMS and are singlets unless otherwise specified. Mass spectroscopy was carried out on a Kratos MS-80, using -CI and EI techniques.

Microanalyses were carried out by Professor A. D. Campbell and associates, University of Otago.

Preparative scale chromatography was routinely carried out utilising a Chromatotron (a preparative scale, centrifugally accelerated, radial, thin layer chromatograph. Model 7924, Harrison Research Inc.) equipped with rotors coated with either Silica gel PF-254 (with $2\text{CaSO}_4 \cdot \text{H}_2\text{O}$ type 60 for tlc, Merck: E. M. Laboratories Inc., Item No. 7749) or Silica gel PF-254/Polyethylene glycol (MW 6000) mixtures.

Except for acetic anhydride (AR grade) all solvents were further purified, usually by distillation over a drying agent. Pyridine was stored over potassium hydroxide pellets, and diethyl ether was stored over sodium wire. Sodium acetate was dried under reduced pressure at 100° for six h., and stored *in vacuo*.

6.2 EXPERIMENTAL RELATING TO CHAPTER TWO

6.2.1 Preparation of 4,6-Dichloro-2,6-dimethylcyclohexa-2,4-dienone (44):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 4-chloro-2,6-dimethylphenol (43) (532 mg) in carbon tetrachloride (5 ml) and pyridine (1 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a yellow oil (650 mg) shown (¹H n.m.r.) to be essentially pure 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44), ν_{\max} (liquid film) 1683, C=O; 1637, C=C; 1590 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.758, s, 6-Me; 1.987, s, 2-Me; 6.333, d, $J_{\text{H5,H3}}$ 1.5Hz, H5; 6.714, d, $J_{\text{H3,H5}}$ 1.5Hz, H3. ¹³C n.m.r. (CDCl₃) δ 15.46, 6-Me; 26.44, 2-Me; 128.23, C6; 134.00, C3 or C5; 134.86, C4; 138.58, C5 or C3; 141.51, C2; 193.67, C1. λ_{\max} (cyclohexane) 235 nm (ϵ 4280). NOe experiments gave the following results: irradiation at 6.714 gave an enhancement at 1.987 (1.4%); irradiation at 6.333 gave an enhancement at 1.758 (0.4%); irradiation at 1.987 gave an enhancement at 6.714 (2.5%); irradiation at 1.758 gave an enhancement at 6.333 (2.8%). This compound was identical with authentic material.¹⁸

Addition of Chlorine to 4,6-Dichloro-2,6-dimethylcyclohexa-2,4-dienone (44):

6.2.1.1 (a) *In Acetic Acid Solution*

To a stirred solution of 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) (320 mg) in acetic acid (5 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 1 h. Removal of the solvent and excess chlorine under reduced pressure gave an oil

(441 mg) shown (^1H n.m.r.) to be a mixture (1 : 3 : 2 : 1) of four compounds which were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *r*-2,4,*t*-5,*c*-6-Tetrachloro-2,6-dimethylcyclohex-3-enone (37), an oil, ν_{max} (liquid film) 1745, C=O; 1649 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.807, s, 2-Me; 1.867, s, 6-Me; 4.640, d, $J_{\text{H5},\text{H3}}$ 1.5Hz, H5; 6.205, d, $J_{\text{H3},\text{H5}}$ 1.5Hz, H3. This compound was identical with authentic material.²⁹

(ii) *r*-2,4,*c*-5,*t*-6-Tetrachloro-2,6-dimethylcyclohex-3-enone (38), an oil, ν_{max} (liquid film) 1746, C=O; 1651 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.918, s, 6-Me; 2.004, s, 2-Me; 4.656, d, $J_{\text{H5},\text{H3}}$ 1.5Hz, H5; 6.185, d, $J_{\text{H3},\text{H5}}$ 1.5Hz, H3. ^{13}C n.m.r. (CDCl_3) δ 23.69, 6-Me; 31.48, 2-Me; 63.55, C2 or C6; 64.86, C5; 67.05, C6 or C2; 131.25, C3; 131.94, C4; 194.60, C1. This compound was identical with authentic material.²⁹

(iii) *trans*-4,4,5,6-Tetrachloro-2,6-dimethylcyclohex-2-enone (45), an oil (Found: C, 36.9; H, 3.3; Cl, 54.3. $\text{C}_8\text{H}_8\text{Cl}_4\text{O}$ requires C, 36.7; H, 3.1; Cl, 54.1%). ν_{max} (liquid film) 1704, C=O; 1640 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.833, s, 6-Me; 1.988, d, $J_{2\text{-Me},\text{H3}}$ 1.45Hz, 2-Me; 5.015, s, H5; 7.017, d, $J_{\text{H3},2\text{-Me}}$ 1.45Hz, H3. λ_{max} (cyclohexane) 232 nm (ϵ 7850). ^{13}C n.m.r. (CDCl_3) δ 16.04, 6-Me; 23.63, 2-Me; 72.81, C6; 73.96, C5; 82.64, C4; 131.31, C2; 142.15, C3; 190.52, C1.

(iv) *r*-2-Acetoxy-4,*c*-5,*t*-6-trichloro-2,6-dimethylcyclohex-3-enone (46), m.p. 125-125.5° (Found C, 42.1; H, 3.8; Cl, 37.5. $\text{C}_{10}\text{H}_{11}\text{O}_3\text{Cl}_3$ requires C, 42.1; H, 3.9; Cl, 37.3%. X-ray crystal structure determined - see Appendix One). ν_{max} (KBr disk) 1740, C=O; 1735, C=O; 1660, C=C; 1230 cm^{-1} , acetate. ^1H n.m.r. (CDCl_3) δ 1.800, s, 2-Me; 1.938, s, 6-Me; 2.064, s, OAc; 4.896, s, H5; 5.962, s, H3. ^{13}C n.m.r. (CDCl_3) δ 20.31, 6-Me; 24.35, 2-Me; 27.25, OCOMe; 66.01, C5; 67.59, C2; 76.18, C6; 129.04, C3; 132.79, C4; 169.17, OCOMe; 194.12, C1. NOe experiments gave the following results: irradiation at 5.962 gave an enhancement at 1.800 (0.2%); irradiation at 4.896 gave an enhancement at 1.938 (0.07%); irradiation at 1.938 gave an enhancement at 4.896 (5.5%); irradiation at

1.800 gave an enhancement at 5.962 (5.6%). This compound was identical with authentic material.²⁵

6.2.1.2 (b) *In Acetic Acid Containing Sodium Acetate*

To a stirred solution of 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) (270 mg) and sodium acetate (1 mole equivalent) in acetic acid (5 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 1 h. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (420 mg) shown (¹H n.m.r.) to be a mixture (3 : 1 : 3) of *r*-2,4,*c*-5,*t*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (38), *trans*-4,4,5,6-tetrachloro-2,6-dimethylcyclohex-2-enone (45) and *r*-2-acetoxy-4,*c*-5,*t*-6-trichloro-2,6-dimethylcyclohex-3-enone (46).

6.2.1.3 (c) *In Acetic Anhydride Solution*

Chlorine was bubbled through a stirred solution of 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) (620 mg) in acetic anhydride (5 ml) for 15 min. in a darkened flask at -10°, and the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a pale yellow oil (820 mg) shown (¹H n.m.r.) to be a mixture (10 : 3 : 2 : 1) of *r*-2,4,*c*-5,*t*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (38), *r*-2-acetoxy-4,*c*-5,*t*-6-trichloro-2,6-dimethylcyclohex-3-enone (46), *trans*-4,4,5,6-tetrachloro-2,6-dimethylcyclohex-2-enone (45) and *r*-2,4,*t*-5,*c*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (37).

6.2.1.4 Treatment of *r*-2,4,*t*-5,*c*-6-Tetrachloro-2,6-dimethylcyclohex-3-enone (37) with Chlorine in Acetic Acid Containing Sodium Acetate:

To a stirred solution of *r*-2,4,*t*-5,*c*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (37) (20 mg) and sodium acetate (1 mole equivalent) in acetic acid (2 ml) at 20° was added a solution of chlorine (0.1 mole equivalent) in acetic acid, and the mixture stirred in a darkened flask for 1 h. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (20 mg) shown (¹H n.m.r.) to be unreacted ketone (37).

6.2.1.5 Treatment of *trans*-4,4,5,6-Tetrachloro-2,6-dimethylcyclohex-2-enone (45) with Chlorine in Acetic Acid Containing Sodium Acetate:

To a stirred solution of *trans*-4,4,5,6-tetrachloro-2,6-dimethylcyclohex-2-enone (45) (20 mg) and sodium acetate (1 mole equivalent) in acetic acid (2 ml) at 20° was added a solution of chlorine (0.1 mole equivalent) in acetic acid, and the mixture stirred in a darkened flask for 1 h. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (20 mg) shown (¹H n.m.r.) to be unreacted ketone (45).

6.2.2 Preparation of a Mixture of 4,5,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) and 3,4,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (48):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 3,4-dichloro-2,6-dimethylphenol (500 mg) in carbon tetrachloride (5 ml) and pyridine (1.0 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with

carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a yellow oil (680 mg) shown (^1H n.m.r.) to be a mixture of the isomeric 6-chlorocyclohexa-2,4-dienones which could not be separated by chromatography. The products were identified from their ^1H n.m.r. spectra.

4,5,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) (c. 60%). ^1H n.m.r. (CDCl_3) δ 1.900, s, 6-Me; 2.007, d, $J_{2-\text{Me},\text{H}3}$ 1.5Hz, 2-Me; 6.854, q, $J_{\text{H}3,2-\text{Me}}$ 1.5Hz, H3. NOe experiments gave the following results: irradiation at 6.854 gave an enhancement at 2.007 (0.5%); irradiation at 2.007 gave an enhancement at 6.854 (2.6%).

3,4,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) (c. 40%). ^1H n.m.r. (CDCl_3) δ 1.777, s, 6-Me; 2.149, d, $J_{2-\text{Me},\text{H}5}$ 0.8Hz, 2-Me; 6.530, q, $J_{\text{H}5,2-\text{Me}}$ 0.8Hz, H5. NOe experiments gave the following results: irradiation at 6.530 gave an enhancement at 1.777 (0.3%); irradiation at 1.777 gave an enhancement at 6.530 (2.8%). This mixture was identical with authentic material.²⁵

Addition of Chlorine to the Mixture (c. 3 : 2) of 4,5,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) and 3,4,6-Trichloro-2,6-dimethylcyclohexa-2,4-dienone (48):

6.2.2.1 (a) *In Acetic Acid Solution*

To a solution of the mixture of trichloro dienones (48) and (49) (600 mg) in acetic acid (4 ml) was added chlorine (1.2 mole equivalents) as a solution in acetic acid. The mixture was stirred in a darkened flask for 6 h. at 20° , and the solvent and excess chlorine were then removed under reduced pressure. The residue (680 mg) was shown (^1H n.m.r.) to be a mixture (6 : 7) of two compounds, which were separated by chromatography on a silica gel Chromatotron plate at 4° to give in order of elution:

(i) *r*-2,3,4,*t*-5,*c*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (50), m.p. 82-83°. ν_{\max} (KBr disk) 1750, C=O; 1625 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.903, s, 2-Me; 1.923, s, 6-Me; 4.806, s, H5. This compound is identical with authentic material.²⁹

(ii) *r*-2,3,4,*c*-5,*t*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (51), m.p. 124-126° (X-ray crystal structure determined - see Appendix 1). ν_{\max} (KBr disk) 1760, C=O; 1615 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.941, s, 6-Me; 2.122, s, 2-Me; 4.819, s, H5. ^{13}C n.m.r. (CDCl_3) δ 23.57, 6-Me; 30.50, 2-Me; 63.95, C5; 66.75, C2 or C6; 67.24, C2 or C6; 129.84, C4; 135.22, C3; 193.02, C1. This compound is identical with authentic material.²⁹

6.2.2.2 (b) In Acetic Acid Containing Sodium Acetate

To a stirred solution of the trichloro dienone mixture (508 mg) in acetic acid (4 ml) containing sodium acetate (1.0 mole equivalent) was added chlorine (1.2 mole equivalents) as a solution in acetic acid. The mixture was stirred in a darkened flask for 40 h. at 20°, then removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (600 mg) shown (^1H n.m.r.) to be a mixture (1 : 1 : 1 : 7 : 1 : 10 : 3) of seven compounds. Chromatography of this oil on a silica gel Chromatotron plate gave in order of elution:

(i) *r*-2,3,4,*t*-5,*c*-6-Pentachloro-2-chloromethyl-6-methylcyclohex-3-enone (52), m.p. 103-105° (X-ray crystal structure determined - see Appendix 1). ν_{\max} (KBr disk) 1746, C=O; 1622 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.942, s, 6-Me; 4.009, 4.356, AB-quartet, $J_{\text{H,H}}$ 11Hz, CH_2Cl ; 4.902, s, H5.

(ii) *r*-2,3,4,*c*-5,*t*-6-Pentachloro-2-chloromethyl-6-methylcyclohex-3-enone (53), isolated only in admixture with its C2 epimer (52). ^1H n.m.r. (CDCl_3 ; by subtraction) δ 2.014, s, 6-Me; 4.171, 4.302, AB-quartet, $J_{\text{H,H}}$ 11Hz, CH_2Cl ; 4.905, s, H5.

(iii) *r*-2,3,4,*t*-5,*c*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (50), m.p. 82-83°, identical with authentic material.²⁹

(iv) *r*-2,3,4,*c*-5,*t*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (51), m.p. 124-126°, identical with authentic material.²⁹

(v) *trans*-3,4,4,5,6-Pentachloro-2,6-dimethylcyclohex-2-enone (54), an oil, isolated only in an impure state. ν_{\max} (liquid film) 1712, C=O; 1607 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.854, s, 6-Me; 2.157, s, 2-Me; 5.085, s, H5.

(vi) *r*-2-Acetoxy-3,4,*c*-5,*t*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (56), m.p. 83-86° (Found M⁺ 319.9362, C₁₀H₁₀O₃³⁵Cl₃³⁷Cl requires 319.9355; X-ray crystal structure determined - see Appendix 1). ν_{\max} (KBr disk) 1748, C=O; 1736 C=O; 1631, C=C; 1232 cm⁻¹, acetate. ¹H n.m.r. (CDCl₃) δ 1.925, s, 2-Me; 1.945, s, 6-Me; 2.105, s, OAc; 5.042, s, H5.

(vii) 3,4,*c*-5,*t*-6-Tetrachloro-*r*-2-hydroxy-2,6-dimethylcyclohex-3-enone (57), m.p. 117-120° (X-ray crystal structure determined - see Appendix 1). ν_{\max} (KBr disk) 3409, OH; 1738, C=O; 1629 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.831, s, 2-Me; 1.903, s, 6-Me; 2.982, br, OH; 4.818, s, H5. NOe experiments gave the following results: irradiation at 1.903 gave an enhancement at 4.818 (3.7%); irradiation at 4.818 gave an enhancement at 1.903 (0.3%).

6.2.2.3 Addition of Chlorine to 3,4-Dichloro-2,6-dimethylphenol in Acetic Anhydride:

Chlorine was bubbled through a stirred solution of 3,4-dichloro-2,6-dimethylphenol (493 mg) in acetic anhydride (5 ml) for 15 min. in a darkened flask at -10°, then the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (654 mg) shown (¹H n.m.r.) to be a mixture (6 : 3 : 2) of *r*-2,3,4,*c*-5,*t*-6-pentachloro-2,6-dimethylcyclohex-3-enone (51), *r*-2-acetoxy-3,4,*c*-5,*t*-6-tetrachloro-2,6-di-

methylcyclohex-3-enone (56) and *r*-2,3,4,*t*-5,*c*-6-pentachloro-2,6-dimethylcyclohex-3-enone (50).

6.2.2.4 Treatment of a Mixture of *r*-2,3,4,*c*-5,*t*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (51) and *r*-2,3,4,*t*-5,*c*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (50) with Chlorine in Acetic Acid Containing Sodium Acetate:

To a stirred solution of a mixture (*c* 4 : 1) of *r*-2,3,4,*c*-5,*t*-6-pentachloro-2,6-dimethylcyclohex-3-enone (51) and *r*-2,3,4,*t*-5,*c*-6-pentachloro-2,6-dimethylcyclohex-3-enone (50) (218 mg) in acetic acid (3 ml) containing sodium acetate (1.0 mole equivalent) was added chlorine (1.2 mole equivalents) as a solution in acetic acid and the mixture stirred at 20° in a darkened flask for 5 h. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (215 mg) shown (¹H n.m.r.) to be identical to an unreacted mixture (*c* 4 : 1) of *r*-2,3,4,*c*-5,*t*-6-pentachloro-2,6-dimethylcyclohex-3-enone (51) and *r*-2,3,4,*t*-5,*c*-6-pentachloro-2,6-dimethylcyclohex-3-enone (50).

6.2.3 Attempted Trapping of Chlorine During [1,5]-Sigmatropic Shift by Phenoxide Ion:

Sodium metal (316 mg) was reacted with methanol (15 ml), and when the reaction was complete the excess methanol was removed under reduced pressure to give sodium methoxide which was dried for 2 h. at 100° under reduced pressure. Sodium methoxide (39 mg) was suspended in pentane (15 ml) and 4-chloro-2,6-dimethylphenol (43) (90 mg) was added, giving a white precipitate, which was filtered off and washed with pentane. This was shown (¹H n.m.r.) to be essentially a single compound:

sodium 4-chloro-2,6-dimethylphenoxide (61), ^1H n.m.r. (d_6 -acetone) δ 2.155, s, 2-Me and 6-Me; 6.770, s, H3 and H5

To a stirred solution of 18-crown-6 (17 mg) in ether (10 ml) in a darkened flask was added sodium 4-chloro-2,6-dimethylphenoxide (61) (10 mg) and a 3 : 2 mixture of 4,5,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (49) and 3,4,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (48) (15 mg) and the mixture was stirred for 2 h. at 20° . Removal of the solvent under reduced pressure gave an emulsion (41 mg) shown (^1H n.m.r.) to be a mixture (c. 16 : 4 : 3 : 2) of 18-crown-6, sodium 4-chloro-2,6-dimethylphenoxide (61), 4,5,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (49), 3,4,6-trichloro-2,6-dimethylcyclohexa-2,4-dienone (48). No 4,6-dichloro-2,6-dimethylcyclohexa-2,4-dienone (44) was detected.

6.3 EXPERIMENTAL RELATING TO CHAPTER THREE

Preparation of 2,4,6-Trichloro-6-methylcyclohexa-2,4-dienone (63):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 2,4-dichloro-6-methylphenol (62) (492 mg) in carbon tetrachloride (5 ml) and pyridine (1 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (590 mg) shown (¹H n.m.r.) to be essentially pure 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (63), (Found M⁺ 211.9354, C₇H₅O³⁵Cl₂³⁷Cl requires 211.9377). ν_{\max} (liquid film) 1699, C=O; 1624, C=C; 1560 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.828, s, 6-Me; 6.421, d, $J_{H5,H3}$ 2.4Hz, H5; 7.134, d, $J_{H3,H5}$ 2.5Hz, H3. This compound is identical with authentic material.⁴⁵

Addition of Chlorine to 2,4,6-Trichloro-6-methylcyclohexa-2,4-dienone (63):

6.3.1 (a) *In Acetic Acid Solution*

To a stirred solution of 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (63) (590 mg) in acetic acid (6 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 6 h. Removal of the solvent and excess chlorine under reduced pressure gave an oil (585 mg) shown (¹H n.m.r.) to be a mixture (3 : 4 : 2) of three compounds which were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *trans*-2,4,5,6,6-Pentachloro-2-methylcyclohex-3-enone (64), not isolated in a pure state. ν_{\max} (Nujol) 1760, C=O; 1654 cm⁻¹, C=C. ¹H n.m.r.

(CDCl₃; by subtraction) δ 1.882, s, 2-Me; 4.946, d, $J_{H5,H3}$ 1.4Hz, H5; 6.203, d, $J_{H3,H5}$ 1.4Hz, H3. This compound is identical with authentic material.³⁹

(ii) *cis*-2,4,5,6,6-Pentachloro-2-methylcyclohex-3-enone (65), m.p. 51-53°. ν_{\max} (KBr disk) 1762, C=O; 1646 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 2.053, s, 2-Me; 4.963, d, $J_{H5,H3}$ 1.5Hz, H5; 6.188, d, $J_{H3,H5}$ 1.5Hz, H3. This compound is identical with authentic material.³⁹

(iii) *trans*-2,4,4,5,6-Pentachloro-6-methylcyclohex-2-enone (66), m.p. 54-57° (Found M⁺ 281.8690, C₇H₅O³⁵Cl₄³⁷Cl requires 281.8754. X-ray crystal structure determined - see Appendix One). ν_{\max} (KBr disk) 1718, C=O; 1615 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.887, s, 6-Me; 5.031, s, H5; 7.418, s, H3). λ_{\max} (cyclohexane) 245 nm (ϵ 9310). This compound is identical with authentic material.²⁵

6.3.2 (b) In Acetic Acid Containing Sodium Acetate

To a stirred solution of 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (63) (631 mg) and sodium acetate (1 mole equivalent) in acetic acid (6 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 24 h. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (774 mg) shown (¹H n.m.r.) to be a mixture (6 : 1 : 1 : 3) of four compounds. These were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *trans*-2,2,4,5,6-Pentachloro-6-methylcyclohex-3-enone (67), an oil (Found M⁺ 281.8753, C₇H₅O³⁵Cl₄³⁷Cl requires 281.8754). ν_{\max} (liquid film) 1759, C=O; 1645 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃): δ 1.947, s, 6-Me; 4.652, d, $J_{H5,H3}$ 1.2Hz, H5; 6.483, d, $J_{H3,H5}$ 1.2Hz, H3.

(ii) *trans*-2,4,5,6,6-Pentachloro-2-methylcyclohex-3-enone (64), identical with authentic material.³⁹

(iii) *cis*-2,4,5,6,6-Pentachloro-2-methylcyclohex-3-enone (65), m.p. 51-53°, identical with authentic material.³⁹

(iv) *trans*-2,4,4,5,6-Pentachloro-6-methylcyclohex-2-enone (66), m.p. 54-57°, identical with authentic material.³⁹

6.3.3 (c) In Acetic Anhydride Solution

Chlorine was bubbled through a stirred solution of 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (63) (480 mg) in acetic anhydride (5 ml) for 15 min. in a darkened flask at -10°, then the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (620 mg) shown (¹H n.m.r.) to be a mixture (21 : 4) of *trans*-2,2,4,5,6-pentachloro-6-methylcyclohex-3-enone (67) and *trans*-2,4,4,5,6-pentachloro-6-methylcyclohex-2-enone (66).

Addition of Chlorine to 2,4-Dibromo-6-methylphenol (68):

6.3.4 (a) In Acetic Acid Solution

To a stirred solution of 2,4-dibromo-6-methylphenol (68) (534 mg) in acetic acid (5 ml) and conc. hydrochloric acid (50μl) at 20° was added a solution of chlorine (1.2 mole equivalents) and the mixture stirred in a darkened flask for 2 h. Removal of the solvent and excess chlorine under reduced pressure gave a residue which was washed with water (20 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (674 mg) shown (¹H n.m.r.) to be a mixture (6 : 3 : 6 : 3 : 1 : 1) of six compounds which

were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *r*-2,4-Dibromo-2,*c*-5,*t*-6-trichloro-6-methylcyclohex-3-enone (69), an oil. ν_{\max} (liquid film) 1757, C=O; 1638 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.950, s, 6-Me; 4.741, d, $J_{\text{H5},\text{H3}}$ 1.5Hz, H5; 6.676, d, $J_{\text{H3},\text{H5}}$ 1.5Hz, H3.

(ii) *r*-2,4-Dibromo-2,*t*-5,*c*-6-trichloro-6-methylcyclohex-3-enone (70), m.p. 53-55° (X-ray crystal structure determined - see Appendix 1). ν_{\max} (KBr disk) 1752, C=O; 1632 cm^{-1} , C=C; ^1H n.m.r. (CDCl_3) δ 1.928, s, 6-Me; 4.732, d, $J_{\text{H5},\text{H3}}$ 1Hz, H5; 6.776, d, $J_{\text{H3},\text{H5}}$ 1Hz, H3.

(iii) 4,*r*-6-Dibromo-2,*c*-5,*t*-6-trichloro-2-methylcyclohex-3-enone (71), not isolated in a pure state. ^1H n.m.r. (CDCl_3) δ 1.867, s, 3H, 2-Me; 5.107, s, H5; 6.391, s, H3.

(iv) 4,*r*-6-Dibromo-*t*-2,*t*-5,6-trichloro-2-methylcyclohex-3-enone (72), m.p. 58-62° (X-ray crystal structure determined - see Appendix 1). ν_{\max} (KBr disk) 1758, C=O; 1644 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.110, s, 6-Me; 5.120, d, $J_{\text{H5},\text{H3}}$ 1.5Hz, H5; 6.375, d, $J_{\text{H3},\text{H5}}$ 1.5Hz, H3.

(v) 2,*r*-4-Dibromo-4,*t*-5,*c*-6-trichloro-6-methylcyclohex-2-enone (73), an oil. ν_{\max} (liquid film) 1718, C=O; 1599 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.900, s, 6-Me; 4.849, s, H5; 7.771, s, H3. λ_{\max} (cyclohexane) 279 nm (ϵ 1820). ^{13}C n.m.r. (CDCl_3) δ 23.35, 6-Me; 70.10, C6; 72.27, C4; 73.54, C5; 120.47, C2; 147.00, C3; 183.60, C1.

(vi) 2,*r*-4-Dibromo-4,*c*-5,*t*-6-trichloro-6-methylcyclohex-2-enone (74), not isolated in a pure state. ^1H n.m.r. (CDCl_3) δ 1.906, s, 6-Me; 4.857, s, H5; 7.532, s, H3.

6.3.5 (b) In Acetic Anhydride Solution

Chlorine was bubbled through a stirred solution of 2,4-dibromo-6-methylphenol (68) (504 mg) in acetic anhydride (5 ml) for 15 min. in a darkened

flask at -10° , and the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a pale yellow oil (691 mg) shown (^1H n.m.r.) to be a mixture (3 : 1) of *r*-2,4-dibromo-2,*t*-5,*c*-6-trichloro-6-methylcyclohex-3-enone (70) and 2,4-dibromo-4,5,6-trichloro-6-methylcyclohex-2-enone (73).

6.3.6 Solvent Effect Study - 2,4,6-Trichloro-6-methylcyclohexa-2,4-dienone (62):

Chlorine was bubbled through a stirred solution of 2,4,6-trichloro-6-methylcyclohexa-2,4-dienone (62) (150 mg) in various mixtures of acetic acid and acetic anhydride (2 ml) for 15 min. in a darkened flask, then the mixture stirred for 2 h. The mixture was diluted with ether (20ml) and washed with water (20 ml), then aqueous saturated sodium bicarbonate (3 x 20 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a residue, the composition of which was determined using ^1H n.m.r.

<u>RATIO OF ACETIC ANHYDRIDE TO ACETIC ACID</u>	<u>TEMP. ($^{\circ}\text{C}$)</u>	<u>% YIELD OF (65)</u>	<u>% YIELD OF (67)</u>	<u>% YIELD OF (66)</u>
9 : 1	-10	4	77	19
1 : 1	-10	4	77	19
1 : 9	-10	7	69	24
1 : 19	20	6	66	28
1 : 49	20	8	66	26
1 : 99	20	10	67	23

6.4 EXPERIMENTAL RELATING TO CHAPTER FOUR

6.4.1 Preparation of 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 2,4,5-trichloro-6-methylphenol (83) (496 mg) in carbon tetrachloride (5 ml) and pyridine (1 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (540 mg) shown (¹H n.m.r.) to be essentially pure 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85), (Found M⁺ 245.8985, C₇H₄O³⁵Cl₃³⁷Cl requires 245.8987). ν_{\max} (liquid film) 1702, C=O; 1613, C=C; 1551 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.971, s, 6-Me; 7.276, s, H₃. λ_{\max} (cyclohexane) 250, 348 nm, ϵ 4800, 1819.

Addition of Chlorine to 2,4,5,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (85):

6.4.1.1 (a) In Acetic Acid Solution

To a stirred solution of 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85) (540 mg) in acetic acid (5 ml) and conc. hydrochloric acid (50 μ l) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 2 h. Removal of the solvent and excess chlorine under reduced pressure gave a solid (714 mg) shown (¹H n.m.r.) to be a mixture (4 : 6) of two compounds which were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *trans*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (86), m.p. 87-88° (Found M^+ 315.8364, $C_7H_4O^{35}Cl_5^{37}Cl$ requires 315.8366). ν_{\max} (KBr disk) 1765, $C=O$; 1618 cm^{-1} , $C=C$. 1H n.m.r. ($CDCl_3$) δ 1.994, s, 2-Me; 5.118, s, H5. This compound was identical with authentic material.²⁹

(ii) *cis*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (87), m.p. 116-118° (Found M^+ 315.8365, $C_7H_4O^{35}Cl_5^{37}Cl$ requires 315.8364). ν_{\max} (KBr disk) 1765, $C=O$; 1620 cm^{-1} , $C=C$. 1H n.m.r. ($CDCl_3$) δ 2.168, s, 2-Me; 5.132, s, H5. This compound was identical with authentic material.²⁹

6.4.1.2 (b) In Acetic Acid Containing Sodium Acetate

To a stirred solution of 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85) (572 mg) and sodium acetate (1 mole equivalent) in acetic acid (6 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 14 days. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave a solid (622 mg) shown (1H n.m.r.) to be a mixture (1 : 2 : 4 : 3) of four compounds of which two could not be separated by chromatography:

(i) *trans*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (86), m.p. 87-88°, identical with authentic material.²⁹

(ii) *cis*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (87), m.p. 116-118°, identical with authentic material.²⁹

(iii) 2-acetoxy-2,4,5,5,6-pentachloro-6-methylcyclohex-3-enone (88), 1H n.m.r. ($CDCl_3$) δ 2.026, s, Me; 2.132, s, Me; 6.125, s, H.

(iv) 2-acetoxy-2,4,5,5,6-pentachloro-6-methylcyclohex-3-enone (89), 1H n.m.r. ($CDCl_3$) δ 2.161, s, Me; 2.166, s, Me; 6.126, s, H.

6.4.1.3 (c) In Acetic Anhydride Solution

Chlorine was bubbled through a stirred solution of 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85) (492 mg) in acetic anhydride (5 ml) for 15 min. in a darkened flask at 20°, and the mixture stirred for 72 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (512 mg) shown (¹H n.m.r.) to be a mixture of unreacted 2,4,5,6-tetrachloro-6-methylcyclohexa-2,4-dienone (85) (60%) and four other compounds which were separated by chromatography on a silica gel/polyethylene glycol Chromatotron plate to give in order of elution:

(i) *trans*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (86) (9%), m.p. 87-88°, identical with authentic material.²⁹

(ii) *cis*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (87) (18%), m.p. 116-118°, identical with authentic material.²⁹

(iii) 2,2,4,5,5,6-Hexachloro-6-methylcyclohex-3-enone (94) (42%), an oil (Found M⁺ 315.8365, C₇H₄O³⁵Cl₅³⁷Cl requires 315.8364). ν_{\max} (KBr disk) 1768, C=O; 1628 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 2.171, s, 6-Me; 6.527, s, H₃.

(iv) 2,4,4,5,5,6-Hexachloro-6-methylcyclohex-2-enone (95) (31%), an oil. ν_{\max} (KBr disk) 1720, C=O; 1612 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 2.165, s, 6-Me; 7.397, s, H₃. λ_{\max} (cyclohexane) 252, 214 nm (ϵ 8760, 13210).

6.4.1.4 Treatment of *cis*-2,3,4,5,6,6-Hexachloro-2-methylcyclohex-3-enone (87) with Sodium Acetate in Acetic Acid:

A solution of *cis*-2,3,4,5,6,6-hexachloro-2-methylcyclohex-3-enone (87) (28 mg) in acetic acid (2 ml) containing sodium acetate (0.1 mole equivalent) at 20° was stirred in a darkened flask for 14 days. Removal of the solvent under reduced

pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave a solid (27 mg) shown (^1H n.m.r.) to be identical with the starting ketone (87).

6.4.2 Preparation of 2,3,4,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (100):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 2,3,4-trichloro-6-methylphenol (84) (512 mg) in carbon tetrachloride (5 ml) and pyridine (1 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a solid (591 mg) shown (^1H n.m.r.) to be essentially pure 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100), m.p. $52-53^\circ$ (Found 245.8986, $\text{C}_7\text{H}_4^{35}\text{Cl}_3^{37}\text{ClO}$ requires 245.8987). ν_{max} (KBr disk) 1685, $\text{C}=\text{O}$; 1611, $\text{C}=\text{C}$; 1531 cm^{-1} , $\text{C}=\text{C}$. ^1H n.m.r. (CDCl_3) δ 1.846, s, 6-Me; 6.615, s, H5. λ_{max} (cyclohexane) 332, 246, 216 nm (ϵ 1480, 5090, 7580).

Addition of Chlorine to 2,3,4,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (100):

6.4.2.1 (a) In Acetic Acid Solution

To a stirred solution of 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100) (136 mg) in acetic acid (5 ml) and conc. hydrochloric acid (50 μl) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 14 days. Removal of the solvent and excess chlorine under reduced pressure gave a solid (158 mg) shown (^1H n.m.r.) to be

essentially pure *trans*-2,2,3,4,5,6-hexachloro-6-methylcyclohex-3-enone (101), m.p. 109-111° (Found M^+ 315.8370, $C_7H_4O^{35}Cl_5^{37}Cl$ requires 315.8364). ν_{\max} (KBr disk) 1758, C=O; 1618 cm^{-1} , C=C. 1H n.m.r. ($CDCl_3$) δ 1.976, s, 6-Me; 4.825, s, H5. ^{13}C n.m.r. ($CDCl_3$) δ 23.71, 6-Me; 63.50, C5; 64.70, C6; 71.29, C2; 131.47, C3 or C4; 133.34, C3 or C4; 186.81, C1. This compound was identical with authentic material.²⁵

6.4.2.2 (b) In Acetic Acid Containing Sodium Acetate

To a stirred solution of 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100) (183 mg) and sodium acetate (1 mole equivalent) in acetic acid (5 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 14 days. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (201 mg) shown (1H n.m.r.) to be unreacted 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100) and a mixture (5 : 4) of two compounds which were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *trans*-2,2,3,4,5,6-Hexachloro-6-methylcyclohex-3-enone (101), m.p. 109-111°, identical with authentic material.²⁵

(ii) *trans*-2,3,4,4,5,6-Pentachloro-6-methylcyclohex-2-enone (102), an oil (Found M^+ 315.8364, $C_7H_4O^{35}Cl_5^{37}Cl$ requires 315.8364). ν_{\max} (liquid film) 1719, C=O; 1675 cm^{-1} , C=C. 1H n.m.r. ($CDCl_3$) δ 1.911, s, 6-Me; 5.110, s, H5. λ_{\max} (cyclohexane) 256, 214 nm (ϵ 10990, 4830).

6.4.2.3 (c) In Acetic Anhydride Solution

Chlorine was bubbled through a stirred solution of 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100) (591 mg) in acetic anhydride (5 ml) for 15

min. in a darkened flask at -10° , and the mixture stirred for 4 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (640 mg) shown (^1H n.m.r.) to be a mixture (10 : 1 : 3 : 3 : 1) of five compounds which were separated by chromatography on a silica gel/polyethylene glycol Chromatotron plate to give in order of elution:

(i) *trans*-2,2,3,4,5,6-Hexachloro-6-methylcyclohex-3-enone (101), m.p. 109-111 $^{\circ}$, identical with authentic material.²⁵

(ii) unidentified ketone (103), m.p. 45-47 $^{\circ}$; ν_{max} (KBr disk) 1712, C=O; 1573 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ , 1.940, s, Me; 4.201, s, H. λ_{max} (cyclohexane) 273 nm (ϵ 6150).

(iii) 2,3,4,4-Tetrachloro-6-methylcyclohexa-2,5-dienone (104), an oil (Found M^+ 245.8987, $\text{C}_7\text{H}_4\text{O}^{35}\text{Cl}_3^{37}\text{Cl}$ requires 245.8986). ν_{max} (liquid film) 1677, C=O; 1586 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.044, d, $J_{6-\text{Me},\text{H}5}$ 1.5Hz, 6-Me; 7.061, q, $J_{\text{H}5,6-\text{Me}}$ 1.5Hz, H5. λ_{max} (cyclohexane) 252, 211 nm (ϵ 8180, 7420).

(iv) *trans*-2,3,4,4,5,6-Pentachloro-6-methylcyclohex-2-enone (102), an oil, identical with authentic material. Sect. 6.4.2.2

(v) 2,3,4,4,5-Pentachloro-6-methylcyclohexa-2,5-dienone (105), m.p. 190-194 $^{\circ}$. ν_{max} (KBr disk) 1690, C=O; 1667 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.298, s, 6-Me. λ_{max} (cyclohexane) 282, 274 nm (ϵ 12410, 9570).

6.4.2.4 Treatment of *trans*-2,3,4,4,5,6-Pentachloro-6-methylcyclohex-2-enone (102) with Acetic Anhydride:

A solution of *trans*-2,3,4,4,5,6-pentachloro-6-methylcyclohex-2-enone (102) (30 mg) in acetic anhydride was stirred in a darkened flask at -10° for 4 h. The mixture was diluted with ether (10ml) and washed with water (10 ml), then

aqueous saturated sodium bicarbonate (4 x 10ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (31 mg) shown (^1H n.m.r.) to be a mixture (c. 2 : 3 : 20) of 2,3,4,4-tetrachloro-6-methylcyclohexa-2,5-dienone (104) (8%), 2,3,4-trichloro-6-methylphenol (84) (12%) and *trans*-2,3,4,4,5,6-pentachloro-6-methylcyclohex-2-enone (102) (80%).

6.4.2.5 Treatment of 2,3,4,6-Tetrachloro-6-methylcyclohexa-2,4-dienone (100) with Acetic Anhydride:

A solution of 2,3,4,6-tetrachloro-6-methylcyclohexa-2,4-dienone (100) (30 mg) in acetic anhydride was stirred in a darkened flask at -10° for 4 h. The mixture was diluted with ether (10ml) and washed with water (10 ml), then aqueous saturated sodium bicarbonate (4 x 10ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (27 mg) shown (^1H n.m.r.) to be a mixture of 2,3,4,4-tetrachloro-6-methylcyclohexa-2,4-dienone (100) (72%), 2,3,4-trichloro-6-methylphenol (84) (3%), the unidentified ketone (103) (11%), 2,3,4,4-tetrachloro-6-methylcyclohexa-2,5-dienone (104) (4%) and 2,3,4,4,5-pentachloro-6-methylcyclohexa-2,5-dienone (105) (10%).

6.5 EXPERIMENTAL RELATING TO CHAPTER FIVE

6.5.1 Preparation of 2,4,6-Trichloro-5,6-dimethylcyclohexa-2,4-dienone (33):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 2,4-dichloro-5,6-dimethylphenol (108) (519 mg) in carbon tetrachloride (5 ml) and pyridine (1 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (754 mg) shown (¹H n.m.r.) to be essentially pure 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33), ν_{\max} (liquid film) 1698, C=O; 1624, C=C; 1571 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.833, s, 6-Me; 2.161, s, 5-Me; 7.203, s, H₃. This compound was identical with authentic material.²⁵

Addition of Chlorine to 2,4,6-Trichloro-5,6-dimethylcyclohexa-2,4-dienone (33):

6.5.1.1 (a) *In Acetic Acid Solution*

To a stirred solution of 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) (506 mg) in acetic acid (5 ml) containing conc. hydrochloric acid (50 μ l) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 3 h. Removal of the solvent and excess chlorine under reduced pressure gave a solid (566 mg) shown (¹H n.m.r.) to be a mixture (2 : 5) of two compounds which were separated by chromatography on a silica gel Chromatotron plate to give in order of elution:

(i) *trans*-2,4,5,6,6-Pentachloro-2,3-dimethylcyclohex-3-enone (35), m.p. 84-86°. ν_{\max} (KBr disk) 1760, C=O; 1641 cm⁻¹, C=C. ¹H n.m.r. (CDCl₃) δ 1.882,

s, 2-Me; 2.119, s, 3-Me; 5.011, s, H5. This compound was identical with authentic material.²⁵

(ii) *cis*-2,4,5,6,6-Pentachloro-2,3-dimethylcyclohex-3-enone (34), m.p. 131-133° (Found M^+ 295.8907, $C_8H_7O^{35}Cl_4^{37}Cl$ requires 295.8910). ν_{\max} (KBr disk) 1768, C=O; 1640 cm^{-1} , C=C; 1H n.m.r. ($CDCl_3$) δ 2.054, s, 2-Me; 2.104, s, 3-Me; 5.044, s, H5. ^{13}C n.m.r. ($CDCl_3$) δ 16.29, 2-Me; 29.91, 3-Me; 66.93, C5; 67.53, C2; 83.80, C6; 118.63, C3; 136.47, C4; 188.21, C1. This compound was identical with authentic material.²⁵

6.5.1.2 (b) In Acetic Acid Containing Sodium Acetate

To a stirred solution of 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) (620 mg) and sodium acetate (1.2 mole equivalents) in acetic acid (5 ml) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid and the mixture stirred in a darkened flask for 72 h. Removal of the solvent and excess chlorine under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (784 mg) shown (1H n.m.r.) to be a mixture (10 : 3 : 1 : 1 : 6) of five compounds. These were separated by chromatography on a silica gel Chromatotron plate, in order of elution:

(i) *trans*-2,2,4,5,6-Pentachloro-5,6-dimethylcyclohex-3-enone (111), m.p. 33-37° (Found M^+ 295.8909, $C_8H_7O^{35}Cl_4^{37}Cl$ requires 295.8910). ν_{\max} (KBr disk) 1761, C=O; 1635 cm^{-1} , C=C. 1H n.m.r. ($CDCl_3$) δ 1.988, s, 6-Me; 2.008, s, 5-Me; 6.503, s, H3. ^{13}C n.m.r. ($CDCl_3$) δ 21.37, 5-Me or 6-Me; 24.07, 5-Me or 6-Me; 70.30, C5 or C6; 70.63, C5 or C6; 74.27, C2; 128.68, C3; 137.59, C4; 188.75, C1.

(ii) *trans*-2,4,4,5,6-Pentachloro-5,6-dimethylcyclohex-2-enone (112), an oil (Found M^+ 295.8911, $C_8H_7O^{35}Cl_4^{37}Cl$ requires 295.8910). ν_{\max} (liquid film) 1726, C=O; 1616 cm^{-1} , C=C. 1H n.m.r. ($CDCl_3$) δ 2.044, s, 6-Me; 2.151, s, 5-Me; 7.074, s, H3. λ_{\max} (cyclohexane) 250nm (ϵ 7450).

(iii) *cis*-2,4,5,6,6-Pentachloro-2,3-dimethylcyclohex-3-enone (34), m.p. 131-133°, identical with authentic material.²⁵

(iv) 2-acetoxy-2,4,5,6-tetrachloro-5,6-dimethylcyclohex-3-enone (113), an oil. ν_{\max} (liquid film) 1767, C=O; 1636, C=C; 1372 cm^{-1} , acetate. ^1H n.m.r. (CDCl_3) δ 1.902, s, Me; 2.110, s, Me; 2.125, s, Me; 6.069, s, H.

(v) unidentified hydroxy ketone (114), an oil (Found M^+ 277.9236, $\text{C}_8\text{H}_8\text{O}_2^{35}\text{Cl}_3^{37}\text{Cl}$ requires 277.9249). ν_{\max} (KBr disk) 2925, O-H; 1754, C=O; 1694 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.069, s, Me; 2.107, s, Me; 4.651, br, OH; 6.678, s, H. λ_{\max} (cyclohexane) 262, 247 nm (ϵ 1300, 950).

6.5.1.3 (c) In Acetic Anhydride Solution

Chlorine was bubbled through a stirred solution of 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) (610 mg) in acetic anhydride (5 ml) for 15 min. in a darkened flask at -10° , and the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a pale yellow oil (660 mg) shown (^1H n.m.r.) to be a mixture (7 : 3) of *trans*-2,2,4,5,6-pentachloro-5,6-dimethylcyclohex-3-enone (111) and *trans*-2,4,4,5,6-pentachloro-5,6-dimethylcyclohex-2-enone (112).

6.5.1.4 Treatment of *trans*-2,2,4,5,6-Pentachloro-5,6-dimethylcyclohex-3-enone (111) With Sodium Acetate in Acetic Acid:

A solution of *trans*-2,2,4,5,6-pentachloro-5,6-dimethylcyclohex-3-enone (111) (30 mg) in acetic acid (2 ml) containing sodium acetate (0.15 mole equivalent) at 20° was stirred in a darkened flask for 24 h. Removal of the solvent under reduced pressure and removal of the sodium acetate by washing a suspension of the residue in ether with water gave an oil (28 mg) shown (^1H n.m.r.) to be unreacted ketone (111).

6.5.1.5 Solvent Effect Study - 2,4,6-Trichloro-5,6-dimethylcyclohexa-2,4-dienone (33):

Chlorine was bubbled through a stirred solution of 2,4,6-trichloro-5,6-dimethylcyclohexa-2,4-dienone (33) (150 mg) in various mixtures of acetic acid and acetic anhydride (2 ml) for 15 min. in a darkened flask, then the mixture stirred for 2 h. The mixture was diluted with ether (20ml) and washed with water (20 ml), then aqueous saturated sodium bicarbonate (3 x 20 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a residue, the composition of which was determined using ^1H n.m.r.

<u>RATIO OF ACETIC ANHYDRIDE TO ACETIC ACID</u>	<u>TEMP. (°C)</u>	<u>% YIELD OF (111)</u>	<u>% YIELD OF (112)</u>	<u>% YIELD OF (34)</u>	<u>% YIELD OF (35)</u>
9 : 1	-10	67	28	3	2
1 : 1	-10	66	29	3	2
1 : 9	-10	65	29	4	2
1 : 19	20	60	32	5	3
1 : 49	20	61	26	8	5
1 : 99	20	57	29	9	5

6.5.2 Addition of Chlorine to 2,4-Dibromo-5,6-dimethylphenol (109):

Chlorine was bubbled through a stirred solution of 2,4-dibromo-5,6-dimethylphenol (109) (320 mg) in acetic anhydride (5 ml) for 15 min. in a darkened flask at -10° , and the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (480 mg) shown (^1H n.m.r.) to be a mixture (3 : 1) of two compounds. These were

separated by chromatography on a silica gel Chromatotron plate in order of elution:

(i) *r*-2,4-Dibromo-2,*t*-5,*c*-6-trichloro-5,6-dimethylcyclohex-3-enone (119), an oil. ν_{\max} (liquid film) 1755, C=O; 1622 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.011, s, Me; 2.016, s, Me; 6.858, s, H.

(ii) 2,*r*-4-Dibromo-4,*t*-5,*c*-6-trichloro-5,6-dimethylcyclohex-2-enone (120), an oil; ν_{\max} (liquid film) 1722, C=O; 1605 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.081, s, Me; 2.188, s, Me; 7.506, s, H. λ_{\max} (hexane) 276 nm (ϵ 3680).

6.5.4 Preparation of 2,4,6-Trichloro-3,6-dimethylcyclohexa-2,4-dienone (17):

A solution of chlorine (1.2 mole equivalents) in carbon tetrachloride (2 ml) was added to a solution of 2,4-dichloro-3,6-dimethylphenol (16) (650 mg) in carbon tetrachloride (5 ml) and pyridine (1 mole equivalent) in a darkened flask and the resulting mixture stirred at 0° for 10 min. The mixture was diluted with carbon tetrachloride (10 ml), then washed with water (50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil (762 mg) shown (^1H n.m.r.) to be essentially pure 2,4,6-trichloro-3,6-dimethylcyclohexa-2,4-dienone (17), ν_{\max} (liquid film) 1681, C=O; 1605, C=C; 1553 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.806, s, 6-Me; 2.388, s, 3-Me; 6.496, s, H₅. λ_{\max} (cyclohexane) 246, 222 nm (ϵ 4570, 10310). This compound was identical with authentic material.¹⁸

Addition of Chlorine to 2,4,6-Trichloro-3,6-dimethylcyclohexa-2,4-dienone (17):

6.5.4.1 (a) *In Acetic Acid Solution*

To a stirred solution of 2,4,6-Trichloro-3,6-dimethylcyclohexa-2,4-dienone (17) (730 mg) in acetic acid (7 ml) containing conc. hydrochloric acid (100 μl) at 20° was added a solution of chlorine (1.2 mole equivalents) in acetic acid

and the mixture stirred in a darkened flask for 1 h. Removal of the solvent and excess chlorine under reduced pressure gave a solid (845 mg) shown (^1H n.m.r.) to be a mixture (7 : 3) of two compounds. These were separated by chromatography on a silica gel Chromatotron plate to give, in order of elution:

(i) *trans*-2,2,4,5,6-Pentachloro-3,6-dimethylcyclohex-3-enone (121), m.p. 130-132° (X-ray crystal structure determined - see Appendix 1). ν_{max} (KBr disk) 1754, C=O; 1643 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.947, s, 6-Me; 2.281, s, 3-Me; 4.725, s, H5. This compound was identical with authentic material.²⁵

(ii) *trans*-2,4,4,5,6-Pentachloro-3,6-dimethylcyclohex-2-enone (55), m.p. 93-95°; ν_{max} (KBr disk) 1715, C=O; 1603 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.867, s, 6-Me; 2.543, s, 3-Me; 5.074, s, H5. λ_{max} (cyclohexane) 251nm (ϵ 9935). This compound was identical with authentic material.²⁵

6.5.4.2 (b) In Acetic Anhydride Solution

Chlorine was bubbled through a stirred solution of 2,4,6-trichloro-3,6-dimethylcyclohexa-2,4-dienone () (760 mg) in acetic anhydride (5 ml) for 15 minutes in a darkened flask at -10°, then the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a solid (970 mg) shown (^1H n.m.r.) to be a mixture (5 : 1) of *trans*-2,2,4,5,6-pentachloro-3,6-dimethylcyclohex-3-enone (121) and *trans*-2,4,4,5,6-pentachloro-3,6-dimethylcyclohex-2-enone (55).

6.5.5 Reaction of 2,4-Dibromo-3,6-dimethylphenol (110) with Chlorine in Acetic Anhydride:

Chlorine was bubbled through a stirred solution of 2,4-dibromo-3,6-dimethylphenol (110) (501 mg) in acetic anhydride (5 ml) for 15 min. in a

darkened flask at -10° , and the mixture stirred for 2 h. The mixture was diluted with ether (30ml) and washed with water (30 ml), then aqueous saturated sodium bicarbonate (4 x 30ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a solid (766 mg) shown (^1H n.m.r.) to be a complex mixture of at least eight compounds. Several compounds could not be isolated by chromatography. The remainder were separated on a silica gel Chromatotron plate in order of elution:

(i) *r*-2,4-Dibromo-2,*t*-5,*c*-6-trichloro-3,6-dimethylcyclohex-3-enone (123) (56%), m.p. $123-125^{\circ}$ (X-ray crystal structure determined - see Appendix 1). ν_{max} (KBr disk) 1748, C=O; 1632 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.932, s, 6-Me; 2.372, s, 3-Me; 4.839, s, H5.

(ii) 2,4-Dibromo-4-chloro-3,6-dimethylcyclohexa-2,5-dienone (124) (6%), an oil. ν_{max} (liquid film) 1661, C=O; 1605 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 2.015, d, $J_{6\text{-Me},\text{H}5} 1.6\text{Hz}$, 6-Me; 2.487, s, 3-Me; 6.970, q, $J_{\text{H}5,6\text{-Me}} 1.6\text{Hz}$, H5. λ_{max} (cyclohexane) 283, 254 nm (ϵ 1370, 7250). ^{13}C n.m.r. (CDCl_3) δ 15.52, 3-Me or 6-Me; 21.58, 6-Me or 3-Me; 77.21, C4; 125.91, C2 or C6; 130.28, C6 or C2; 141.72, C5; 155.80, C3; 177.01, C1.

(iii) 2,*r*-4-Dibromo-4,*c*-5,*t*-6-trichloro-3,6-dimethylcyclohex-2-enone (125) (8%), m.p. $105-107^{\circ}$ (X-ray crystal structure determined - see Appendix 1). ν_{max} (KBr disk) 1698, C=O; 1590 cm^{-1} , C=C. ^1H n.m.r. (CDCl_3) δ 1.901, s, 6-Me; 2.654, s, 3-Me; 4.903, s, H5.

6.5.5.1 Treatment of 2,*r*-4-Dibromo-4,*c*-5,*t*-6-trichloro-3,6-dimethylcyclohex-2-enone (125) with Acetic Anhydride:

15 mg of 2,*r*-4-dibromo-4,*c*-5,*t*-6-trichloro-3,6-dimethylcyclohex-2-enone (125) was dissolved in acetic anhydride (2 ml) and stirred in a darkened flask at -10° for 2h. The mixture was diluted with ether (5 ml) and washed with water (10 ml), then aqueous saturated sodium bicarbonate (3 x 5ml) and

dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a solid (15 mg) shown (^1H n.m.r.) to be essentially unreacted ketone (125).

6.6 SYNTHESSES OF SELECTED PHENOLS

2,4-Dibromo-6-methylphenol (68):

To a stirred solution of *o*-cresol (5.001 g) in acetic acid (50 ml) in a darkened flask was added bromine (15.503 g; 2.1 mole equivalents) as a solution in acetic acid (10 ml) dropwise over 15 min. and the resulting mixture stirred for 2 h. The mixture was poured into water (50 ml), the precipitate filtered off, and a solution in ether dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a solid (7.2 g) shown (^1H n.m.r.) to be essentially pure 2,4-dibromo-6-methylphenol (68), m.p. 52-54°. ν_{max} (KBr disk) 3404, O-H; 1589, 1465 cm^{-1} , Ar. ^1H n.m.r. (CDCl_3) δ 2.271, s, 6-Me; 5.527, br, OH; 7.209, d, $J_{\text{H5,H3}}$ 2.5Hz, H5; 7.432, d, $J_{\text{H3,H5}}$ 2.5Hz, H3. This compound was identical with authentic material.⁵⁰

2,4-Dichloro-6-methylphenol (62):

To a stirred solution of *o*-cresol (10.01 g) in ethanol-free chloroform (100 ml) in a darkened flask was added sulphuryl chloride (27.49 g; 2.2 mole equivalents) as a solution in ethanol-free chloroform (35 ml) dropwise over 15 min. and the resulting mixture stirred for 90 min. The mixture was extracted with aqueous sodium hydroxide (2 M, 60 ml x 4), the aqueous portions combined and precipitated with concentrated hydrochloric acid. The solid was taken into ether and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a residue which was recrystallised from petroleum ether to give a solid (12.02 g) shown (^1H n.m.r.) to be pure 2,4-dichloro-6-methylphenol (62), m.p. 53-55°; ν_{max} (KBr disk) 3385, O-H; 1596, 1469 cm^{-1} , Ar.

^1H n.m.r. (CDCl_3) δ 2.257, s, 6-Me; 5.537, br, OH; 7.030, d, $J_{\text{H5},\text{H3}}$ 2.5Hz, H5; 7.167, d, $J_{\text{H3},\text{H5}}$ 2.5Hz, H3. This compound was identical with authentic material.⁵¹

2,3,4-Trichloro-6-methylphenol (84):

Chlorine was bubbled through a stirred solution of 3-chloro-6-methylaniline (15.20 g) in acetic acid (130 ml) and conc. hydrochloric acid (10 ml) in a darkened flask for 2 h. The excess chlorine was removed by a stream of nitrogen, and the solution filtered. Removal of the solvent under reduced pressure gave a residue (19.84 g) shown (^1H n.m.r.) to be a mixture (c. 1 : 1) of *cis* and *trans* isomers of 2,2,3,4,5,6-hexachloro-6-methylcyclohex-3-enone (101) and (130). Following recrystallisation from petroleum ether, the mixture (8.12 g) was dissolved in acetic acid (130 ml), zinc dust (8.10 g) was added slowly and the mixture stirred for 90 min. at 20°. The mixture was filtered, water (200 ml) added to the filtrate, and extracted with petroleum ether (3 x 100 ml). The organic portions were dried over magnesium sulphate and removal of the solvent under reduced pressure gave a solid (5.46 g) shown (^1H n.m.r.) to be pure 2,3,4-trichloro-6-methylphenol (84), m.p. 78-79°. ν_{max} (KBr disk) 3406, O-H; 1450, Ar; 1377 cm^{-1} , Ar. ^1H n.m.r. (CDCl_3) δ 2.254, s, 6-Me; 5.680, br, OH; 7.175, s, H5. ^{13}C n.m.r. (CDCl_3) δ 16.17, 6-Me; 118.62, 119.50, 124.11, 125.10; C2, C3, C4 and C6; 129.86, C5; 149.37, C1. This compound was identical with authentic material.⁵¹

2,4,5-Trichloro-6-methylphenol (83):

Chlorine was bubbled through a stirred solution of 3-chloro-2-methylaniline in acetic acid (13 ml) and conc. hydrochloric acid (10 ml) in a darkened flask for 2 h. at 20°. The mixture was filtered and a solution in ether washed with water

(50 ml) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a solid (19.31 g) shown to be pure *trans*-2,3,4,5,6,6-hexachloro-2-methylcyclohex-3-enone (86). Following recrystallisation from petroleum ether, the mixture (15.17 g) was dissolved in acetic acid (200 ml), zinc dust (12.73 g) was added slowly and the mixture stirred for 1 h. at 20°. The mixture was filtered, water (200 ml) added to the filtrate, and extracted with petroleum ether (3 x 75 ml). The organic portions were dried over magnesium sulphate and removal of the solvent under reduced pressure gave a solid (10.26 g) shown (¹H n.m.r.) to be pure 2,4,5-trichloro-6-methylphenol (83), m.p. 51-53°. ν_{\max} (KBr disk) 3495, OH; 1571, Ar; 1448 cm⁻¹, Ar. ¹H n.m.r. (CDCl₃) δ 2.382, s, 6-Me; 5.672, br, OH; 7.326, s, H₃. This compound was identical with authentic material.⁵¹

6.7 APPENDIX 1: CRYSTALLOGRAPHY

Crystal data from a Nicolet XRD R3m four circle diffractometer [molybdenum X-radiation, $\lambda(\text{Mo K}\alpha)$ 0.71069 Å, from a crystal monochromator], are given below. In each case, the space group was determined unambiguously by the conditions limiting possible reflections. The ω -scan technique was used to collect reflection intensities out to a maximum Bragg angle θ , at 173 K. The cell parameters were determined by least squares refinements for which the setting angles of 20-25 high angle reflections were used. Absorption corrections were made by a procedure based on azimuthal Ψ -scans.

Crystal data for *r-2,3,4,c-5,t-6-pentachloro-2,6-dimethylcyclohex-3-enone* (51), $\text{C}_8\text{H}_7\text{Cl}_5\text{O}$, M 296.4, monoclinic, space group $P2_1/c$, a 8.480(2), b 9.998(2), c 13.221(3), β 97.93(3)°, V 1110.20(4) Å³, D_c 1.773 g cm⁻³, Z 4, $\mu(\text{Mo K}\alpha)$ 12.78 cm⁻¹. The crystal was colourless and of approximate dimensions 0.40 by 0.30 by 0.10 mm. Number of independent reflections measured 1915, 1220 with $I > 3\sigma(I)$. Maximum Bragg angle θ 25°; g 0.00132; $R_{(\text{obs})}$ -factor 0.0399; $wR_{(\text{all data})}$ 0.0508; absorption correction transmission max. 0.763, min. 0.740.

Crystal data for *r-2,3,4,t-5,c-6-pentachloro-2-chloromethyl-6-methylcyclohex-3-enone* (52), $\text{C}_8\text{H}_6\text{Cl}_6\text{O}$, M 324.8, monoclinic, space group $P2_1/c$, a 8.471(2), b 10.331(2), c 13.564(3), β 95.30(3)°, V 1182.0(4) Å³, D_c 1.825 g cm⁻³, Z 4, $\mu(\text{Mo K}\alpha)$ 14.31 cm⁻¹. The crystal was colourless and of approximate dimensions 0.38 by 0.30 by 0.013 mm. Number of independent reflections measured 2069, 1462 with $I > 2\sigma(I)$. Maximum Bragg angle θ 25°; g 0.0006; $R_{(\text{obs})}$ -factor 0.0652; $wR_{(\text{all data})}$ 0.0988; absorption correction not applied.

Crystal data for *r*-2-acetoxy-3,4,5,6-tetrachloro-2,6-dimethylcyclohex-3-enone (56), $C_{10}H_{10}Cl_4O$, M 320.0, monoclinic, space group $P2_1/c$, a 10.996(9), b 9.253(6), c 12.611(11), β 93.81(7)°, V 1280(2) Å³, D_c 1.660 g cm⁻³, Z 4, μ (Mo K α) 9.20 cm⁻¹. The crystal was colourless and of approximate dimensions 0.52 by 0.48 by 0.30 mm. Number of independent reflections measured 2177, 1676 with $I > 3\sigma(I)$. Maximum Bragg angle θ 25°; g 0.006; $R_{(obs)}$ -factor 0.0335; $wR_{(all\ data)}$ 0.0450; absorption correction not applied.

Crystal data for 3,4,5,6-tetrachloro-2-hydroxy-2,6-dimethylcyclohex-3-enone (57), $C_8H_8Cl_4O_2$, M 278.0, monoclinic, space group $P2_1/c$, a 9.504(3), b 12.582(4), c 9.509(3), β 103.10(2)°, V 1107.5(6) Å³, D_c 1.619 g cm⁻³, Z 4, μ (Mo K α) 10.43 cm⁻¹. The crystal was colourless and of approximate dimensions 0.36 by 0.24 by 0.24 mm. Number of independent reflections measured 1938, 1536 with $I > 2\sigma(I)$. Maximum Bragg angle θ 25°; unit weights; $R_{(obs)}$ -factor 0.0491; $wR_{(all\ data)}$ 0.0553; absorption correction not applied.

Crystal data for *trans*-2,4,4,5,6-pentachloro-6-methylcyclohex-2-enone (66), $C_7H_5Cl_5O$, M 282.4, monoclinic, space group $P2_1/c$, a 18.520(8), b 7.476(3), c 15.708(11), β 100.61(5)°, V 2138(2) Å³, D_c 1.723 g cm⁻³, Z 8, μ (Mo K α) 13.22 cm⁻¹. The crystal was colourless and of approximate dimensions 0.56 by 0.28 by 0.12 mm. Number of independent reflections measured 3767, 2052 with $I > 3\sigma(I)$. Maximum Bragg angle θ 25°; g 0.0008; $R_{(obs)}$ -factor 0.0496; $wR_{(all\ data)}$ 0.0635; absorption correction transmission max. 0.874, min. 0.779.

Crystal data for *r*-2,4-dibromo-2,5,6-trichloro-6-methylcyclohex-3-enone (70), $C_7H_5Br_2Cl_3O$, M 371.28, monoclinic, space group $P2_1/c$, a 7.558(2), b 9.808(2), c 8.364(2), β 112.45(3)°, V 573.0(2) Å³, D_c 2.152 g cm⁻³, Z 4, μ (Mo K α) 77.3 cm⁻¹. The crystal was colourless and of approximate dimensions 0.35 by 0.30 by 0.20 mm. Number of independent reflections measured 1392, 823 with $F_o > 3\sigma(F_o)$.

Maximum Bragg angle θ 27.5°; g 0.1265; $R_{(\text{obs})}$ -factor 0.0859; $wR_{(\text{all data})}$ 0.2099; absorption correction transmission max. 0.678, min. 0.315.

Crystal data for 4,*r*-6-dibromo--*t*-2,*t*-5,6-trichloro-2-methylcyclohex-3-enone (72), $\text{C}_7\text{H}_5\text{Br}_2\text{Cl}_3\text{O}$, M 371.28, monoclinic, space group $P2_1/c$, a 6.315(2), b 22.399(5), c 8.430(4), β 111.30(3)°, V 1111.0(4) Å³, D_c 2.220 g cm⁻³, Z 4, $\mu(\text{Mo K}\alpha)$ 79.8 cm⁻¹. The crystal was colourless and of approximate dimensions 0.35 by 0.30 by 0.15 mm. Number of independent reflections measured 1953, 1234 with $F_o > 2\sigma(F_o)$. Maximum Bragg angle θ 25°; g 0.0630; $R_{(\text{obs})}$ -factor 0.0585; $wR_{(\text{all data})}$ 0.1214; absorption correction transmission max. 0.930, min. 0.506.

Crystal data for trans-2,2,4,5,6-pentachloro-3,6-dimethylcyclohex-3-enone (121), $\text{C}_8\text{H}_7\text{Cl}_5\text{O}$, M 296.4, monoclinic, space group $P2_1/c$, a 8.464(2), b 10.020(2), c 13.296(4), β 98.66(2)°, V 1114.8(5) Å³, D_c 1.766 g cm⁻³, Z 4, $\mu(\text{Mo K}\alpha)$ 12.73 cm⁻¹. The crystal was colourless and of approximate dimensions 0.70 by 0.25 by 0.20 mm. Number of independent reflections measured 2541, 2100 with $I > 3\sigma(I)$. Maximum Bragg angle θ 27.5°; g 0.0004; $R_{(\text{obs})}$ -factor 0.0323; $wR_{(\text{all data})}$ 0.0436; absorption correction not applied.

Crystal data for *r*-2,4-dibromo-2,*t*-5,*c*-6-trichloro-3,6-dimethylcyclohex-3-enone (123), $\text{C}_8\text{H}_7\text{Cl}_3\text{Br}_2\text{O}$, M 385.3, monoclinic, space group $P2_1/c$, a 8.612(2), b 10.164(2), c 13.565(3), β 97.29(3)°, V 1177.8(4) Å³, D_c 2.173 g cm⁻³, Z 4, $\mu(\text{Mo K}\alpha)$ 74.7 cm⁻¹. The crystal was colourless and of approximate dimensions 0.40 by 0.28 by 0.08 mm. Number of independent reflections measured 3428, 1450 with $I > 3\sigma(I)$. Maximum Bragg angle θ 30°; g 0.001; $R_{(\text{obs})}$ -factor 0.0860; $wR_{(\text{all data})}$ 0.1147; absorption correction transmission max. 1.00, min. 0.459.

Crystal data for 2,*r*-4-dibromo-4,*c*-5,*t*-6-trichloro-3,6-dimethylcyclohex-2-enone (125), $\text{C}_8\text{H}_7\text{Cl}_3\text{Br}_2\text{O}$, M 385.3, monoclinic, space group $P2_1/c$, a 8.597(2), b

18.276(4), c 7.933(2), β 106.64(3)°, V 1194.2(5) Å³, D_c 2.143 g cm⁻³, Z 4, $\mu(\text{Mo K}\alpha)$ 73.7 cm⁻¹. The crystal was colourless and of approximate dimensions 0.56 by 0.22 by 0.20 mm. Number of independent reflections measured 1868, 1093 with $I > 2\sigma(I)$. Maximum Bragg angle θ 24°; unit weights; $R_{(\text{obs})}$ -factor 0.0661; $wR_{(\text{all data})}$ 0.0757; absorption correction transmission max. 0.895, min. 0.688.

Structure Determination

The structures were solved by direct methods and difference-Fourier syntheses. Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were introduced at idealised positions with a common thermal parameter and not generally refined. The SHELXTL^{49a} and SHELXTL.PC^{49b} packages were used for data reduction and structure solution. The function minimised was $\Sigma w[|F_o| - |F_c|]^2$ with reflection weights $w = [\sigma^2 |F_o| + g.F_o^2]^{-1}$. For compounds (70) and (72) the SHELXTL-92 package was used,^{49c} where the function minimised was $\Sigma [w(F_o^2 - F_c^2)^2]$ with reflection weights $[\sigma^2(F_o^2) + (g_1.P)^2 + g_2.P]^{-1}$ where $P = [F_o^2 + 2.F_c^2]/3$. Atomic scattering factors from the International Tables for X-ray Crystallography, Vol. iv, 1974 are used in conjunction with the above packages. Final Fourier syntheses show no residual electron density, and there were no abnormal discrepancies between observed and calculated structure factors.

**Table 6.1 Fractional Atomic Coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$) for
r-2,3,4,*c*-5,*t*-6-Pentachloro-2,6-dimethylcyclohex-3-enone (51)**

	x	y	z	U(eq)
Cl(2)	3593(2)	5232(1)	1007(1)	32(1)
Cl(3)	5310(2)	2263(1)	711(1)	30(1)
Cl(4)	2301(2)	418(1)	217(1)	27(1)
Cl(5)	-483(2)	3054(1)	504(1)	29(1)
Cl(6)	2137(2)	1624(1)	3334(1)	25(1)
O(1)	1811(4)	5018(3)	2784(3)	26(1)
C(1)	2075(6)	3976(5)	2387(4)	18(2)
C(2)	3583(6)	3818(4)	1863(4)	19(2)
C(3)	3564(6)	2574(5)	1205(4)	21(2)
C(4)	2314(6)	1790(4)	1007(4)	19(2)
C(5)	758(6)	2044(5)	1407(4)	21(2)
C(6)	1008(6)	2762(4)	2444(4)	19(1)
C(7)	5053(6)	3918(8)	2668(4)	28(2)
C(8)	-531(6)	3110(5)	2848(4)	23(2)

For Tables 6.1 to 6.10 U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 6.2 Atomic Coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$) for *r*-2,3,4,*t*-5,*c*-6-pentachloro-2-chloromethyl-6-methylcyclohex--3-enone (52)

	x	y	z	U(eq)
Cl(2)	10130(4)	1724(3)	3155(2)	31(1)
Cl(3)	10450(3)	2921(3)	922(2)	28(1)
Cl(4)	7385(4)	4540(3)	265(2)	25(1)
Cl(5)	4559(4)	2188(3)	617(2)	28(1)
Cl(6)	6857(4)	3548(3)	3403(2)	25(1)
Cl(7)	7933(4)	-183(3)	589(3)	37(1)
O(1)	6751(9)	216(8)	2830(6)	22(3)
C(1)	7069(13)	1261(11)	2508(8)	17(3)
C(2)	8680(13)	1470(12)	2072(9)	20(4)
C(3)	8656(13)	2621(12)	1386(8)	18(3)
C(4)	7377(14)	3325(11)	1134(8)	18(3)
C(5)	5813(14)	3120(11)	1521(9)	22(4)
C(6)	5936(13)	2390(11)	2522(8)	17(3)
C(7)	9215(16)	219(12)	1631(10)	30(4)
C(8)	4314(14)	2029(12)	2866(9)	23(4)

Table 6.3 Atomic Coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$) for *r*-2-acetoxy-3,4,*c*-5,*t*-6-tetrachloro-2,6-dimethylcyclohex-3-enone (56)

	x	y	z	U(eq)
Cl(3)	7673(1)	-2621(1)	6198(1)	35(1)
Cl(4)	7165(1)	-1389(1)	3917(1)	30(1)
Cl(5)	5836(1)	1822(1)	4481(1)	25(1)
Cl(6)	9694(1)	1976(1)	5318(1)	23(1)
O(1)	8110(3)	2591(3)	7420(2)	29(1)
O(2)	7195(2)	-210(3)	7731(2)	23(1)
O(8)	5810(2)	1181(3)	6845(2)	25(1)
C(1)	8035(3)	1742(4)	6699(3)	18(1)
C(2)	8040(3)	117(4)	6930(3)	19(1)
C(3)	7704(3)	-782(4)	5952(3)	18(1)
C(4)	7462(3)	-280(4)	4989(3)	18(1)
C(5)	7412(3)	1296(4)	4719(3)	17(1)
C(6)	8094(3)	2249(4)	5554(3)	16(1)
C(7)	9290(3)	-305(5)	7454(3)	33(1)
C(8)	5197(4)	-264(4)	8304(3)	28(1)
C(9)	6050(3)	334(4)	7547(3)	20(1)
C(10)	7827(4)	3849(4)	5434(3)	26(1)

Table 6.4 Atomic Coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$) for 3,4,*r*-5,*t*-6-tetrachloro-*c*-2-hydroxy-2,6-dimethylcyclohex-3-enone (57)

	x	y	z	U(eq)
Cl(3)	-2485(1)	1699(1)	2898(1)	38(1)
Cl(4)	-637(2)	3700(1)	4161(2)	41(1)
Cl(5)	1663(2)	3574(1)	1701(2)	32(1)
Cl(6)	2462(1)	1099(1)	4936(1)	28(1)
O(1)	2011(4)	655(3)	1157(4)	23(1)
O(2)	-882(4)	1004(3)	564(3)	22(1)
C(1)	1482(5)	1066(4)	2063(5)	17(1)
C(2)	-132(5)	922(4)	2038(4)	18(1)
C(3)	-693(5)	1818(4)	2830(5)	22(2)
C(4)	73(5)	2661(4)	3362(5)	23(2)
C(5)	1622(5)	2809(4)	3303(5)	21(2)
C(6)	2410(5)	1761(4)	3236(5)	20(2)
C(7)	-360(6)	-183(4)	2628(6)	26(2)
C(8)	3962(5)	1872(5)	3057(6)	27(2)

Table 6.5 Atomic Coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$) for *trans*-2,4,4,5,6-pentachloro-6-methylcyclohex-2-enone (66)

	x	y	z	U(eq)
Cl(1)	-719(1)	5537(3)	8914(1)	43(1)
Cl(21)	1871(1)	7559(3)	10107(1)	43(1)
Cl(22)	1115(1)	10711(3)	9359(2)	60(1)
Cl(3)	2286(1)	8672(3)	8287(1)	45(1)
Cl(4)	1305(1)	5936(3)	6916(1)	47(1)
O(1)	163(3)	4245(9)	7692(4)	63(3)
C(1)	463(4)	5447(10)	8117(4)	32(2)
C(2)	133(3)	6325(9)	8799(4)	26(2)
C(3)	457(4)	7574(10)	9332(5)	28(2)
C(4)	1194(4)	8338(9)	9233(5)	29(2)
C(5)	1378(4)	7968(9)	8330(4)	28(2)
C(6)	1246(4)	6009(9)	8045(4)	26(2)
C(7)	1782(4)	4629(10)	8523(5)	38(3)
Cl(5)	5781(1)	1111(3)	11078(1)	46(1)
Cl(61)	3077(1)	1787(3)	9866(1)	33(1)
Cl(62)	3587(1)	5353(3)	10337(1)	43(1)
Cl(7)	2592(1)	3105(3)	11592(1)	45(1)
Cl(8)	3769(1)	1294(3)	13140(1)	49(1)
O(1a)	5104(3)	296(9)	12564(4)	65(3)
C(1a)	4678(4)	986(10)	11988(5)	33(3)
C(2a)	4897(3)	1621(9)	11192(4)	26(2)
C(3a)	4464(3)	2539(9)	10572(4)	25(2)
C(4a)	3691(4)	3052(9)	10651(4)	26(2)
C(5a)	3550(4)	2861(9)	11585(5)	28(2)
C(6a)	3848(4)	1111(10)	12022(4)	29(2)
C(7a)	3484(4)	-630(10)	11658(5)	39(3)

Table 6.6 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{\AA}^2 \times 10^3$) for *r*-2,4-dibromo-2,*t*-5,*c*-6-trichloro-6-methylcyclohex-2-enone (70)

	x	y	z	U(eq)
Br(2)	7715(8)	5571(5)	7289(9)	91(3)
Br(4)	720(3)	4022(6)	3144(2)	50.3(11)
Cl(2)	7691(8)	2419(5)	7264(8)	25(2)
Cl(5)	2876(19)	1814(8)	7647(15)	72(8)
Cl(6)	2811(20)	6241(7)	7589(19)	61(10)
O(1)	6849(19)	3941(34)	10160(19)	15(7)
C(1)	5678(27)	3962(42)	8746(24)	44(5)
C(2)	6224(28)	3909(35)	7147(23)	43(5)
C(3)	4558(25)	4107(35)	5446(22)	38(4)
C(4)	2799(25)	3973(40)	5304(24)	39(9)
C(5)	2238(36)	3669(25)	6787(29)	46(6)
C(6)	3504(29)	4471(25)	8388(30)	42(9)
C(7)	3187(33)	4182(47)	10054(27)	56(12)

Table 6.7 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{\AA}^2 \times 10^3$) for 4,*r*-6-dibromo-*t*-2,*t*-5,6-trichloro-2-methylcyclohex-3-enone (72)

	x	y	z	U(eq)
Br(4)	-1644(2)	-1671.4(5)	-3752.1(13)	28.8(6)
Br(6)	-3022(2)	-274.3(6)	-7746(2)	39.6(7)
Cl(2)	-7570(6)	-2111.1(14)	-9592(4)	47(2)
Cl(5)	-7703(5)	-1193.0(14)	-5651(4)	35(2)
Cl(6)	-7744(4)	-10.8(12)	-7850(3)	21.6(13)
O(1)	-8372(12)	-913(3)	-10420(9)	31(4)
C(1)	-6777(17)	-1035(5)	-9204(12)	20(6)
C(2)	-5482(18)	-1626(5)	-9074(12)	24(6)
C(3)	-3841(18)	-1760(5)	-7306(12)	21(6)
C(4)	-3704(16)	-1457(5)	-5920(12)	18(5)
C(5)	-5198(16)	-938(4)	-5969(12)	16(5)
C(6)	-5822(16)	-609(4)	-7660(12)	15(5)
C(7)	-4328(22)	-1623(6)	-10389(12)	40(9)

Table 6.8 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{\AA}^2 \times 10^3$) for *trans*-2,2,4,5,6-pentachloro-3,6-dimethylcyclohex-3-enone (121)

	x	y	z	U(eq)
Cl(21)	1351(1)	5211(1)	3953(1)	28(1)
Cl(22)	-266(1)	3838(1)	2160(1)	26(1)
Cl(4)	2742(1)	407(1)	4764(1)	23(1)
Cl(5)	5486(1)	3084(1)	4491(1)	27(1)
Cl(6)	2848(1)	1605(1)	1662(1)	22(1)
O(1)	3148(2)	5019(2)	2214(1)	23(1)
C(1)	2904(3)	3971(2)	2593(2)	17(1)
C(2)	1433(3)	3781(2)	3147(2)	17(1)
C(3)	1375(3)	2545(2)	3785(2)	17(1)
C(4)	2685(3)	1786(2)	3975(2)	16(1)
C(5)	4229(3)	2041(3)	3580(2)	18(1)
C(6)	3989(3)	2854(2)	2551(2)	18(1)
C(7)	-145(3)	2268(3)	4208(2)	24(1)
C(8)	5529(3)	3116(3)	2162(2)	21(1)

Table 6.9 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{\AA}^2 \times 10^3$) for *r*-2,4-dibromo-2,*t*-5,*c*-6-trichloro-3,6-dimethylcyclohex-3-enone (123)

	x	y	z	U(eq)
Br(2)	5249(2)	3885(3)	7860(2)	37(1)
Br(4)	2296(2)	356(2)	5194(2)	32(1)
Cl(2)	3560(4)	5258(4)	6012(3)	11(1)
Cl(5)	-468(5)	3041(5)	5541(3)	26(2)
Cl(6)	2117(5)	1617(4)	8312(3)	13(1)
O(1)	1780(13)	4994(12)	7750(9)	20(4)
C(1)	2040(17)	3978(19)	7379(12)	11(3)
C(2)	3490(18)	3817(18)	6837(12)	13(3)
C(3)	3598(18)	2593(18)	6226(12)	12(4)
C(4)	2280(18)	1856(18)	6046(12)	13(3)
C(5)	815(18)	2054(19)	6417(12)	16(4)
C(6)	1032(18)	2737(18)	7447(12)	13(4)
C(7)	5093(19)	2338(21)	5891(14)	22(4)
C(8)	-519(19)	3098(19)	7827(13)	19(4)

Table 6.10 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{\AA}^2 \times 10^3$) for 2,*r*-4-dibromo-4,*c*-5,*t*-6-trichloro-3,6-dimethylcyclohex-2-enone (125)

	x	y	z	U(eq)
Br(2)	1985(2)	8054(1)	1149(3)	39(1)
Br(4)	-1669(3)	10111(1)	-2729(3)	47(1)
Cl(4)	-1445(5)	8906(3)	-5316(5)	31(2)
Cl(5)	-4871(5)	9022(3)	-4225(6)	32(2)
Cl(6)	-4583(5)	7828(2)	1071(6)	30(2)
O(1)	-1351(14)	7872(7)	1434(15)	31(5)
C(1)	-1443(17)	8212(8)	132(20)	16(5)
C(2)	16(19)	8405(9)	-392(21)	25(6)
C(3)	49(19)	8793(8)	-1853(20)	17(5)
C(4)	-1535(20)	9043(9)	-3071(19)	20(6)
C(5)	-3020(17)	8637(8)	-2892(19)	15(5)
C(6)	-3053(18)	8519(8)	-975(21)	17(5)
C(7)	1599(21)	9004(9)	-2295(26)	31(7)
C(8)	-3459(22)	9187(9)	-37(24)	32(7)

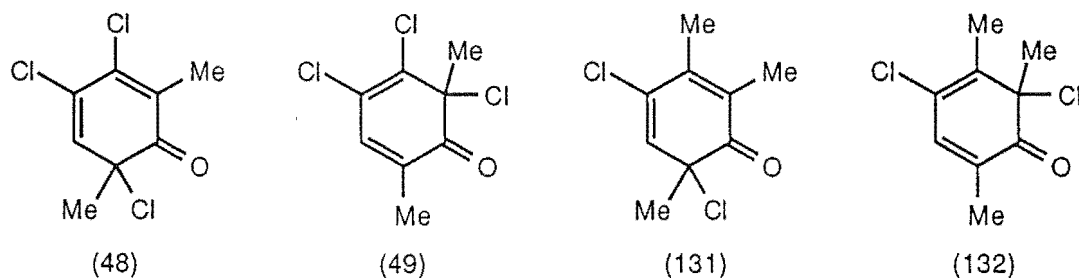
6.8 APPENDIX 2: SEMI-EMPIRICAL CALCULATIONS

Summarised in Table 6.11 (over) are the results of the MOPAC Semi-empirical calculations of the various cyclohexa-2,4-dienones discussed in this thesis. This brief investigation has illustrated some of the deficiencies of the AM1 and PM3 parameter sets in calculating energies for these compounds.

For calculations of ground states compounds both methods are known to reproduce geometries accurately. Stewart reported the average error in bond lengths and angles for a series of compounds with known geometries from crystallography.⁵² These were found to be, for AM1 - bond length 0.050 Å, angle 3.3°, for PM3 - bond length 0.036 Å, angle 3.9°. This paper also reported the error in calculated heats of formation for compounds with measured experimental values. For a series of 32 chlorine containing organic compounds the average errors were found to be less than 25 kJ mol⁻¹ by the AM1 method, and less than 16 kJ mol⁻¹ by the PM3 method. However, the worst case error by these methods was +43.5 kJ mol⁻¹ by AM1 and +35 kJ mol⁻¹ by PM3.⁵² The accuracy of the calculated heats of formation of chlorocyclohexadienones is not known, but it is believed that any errors in the calculations should be consistent.

For transition states the errors in energy are generally higher. Calculated energy barriers are known to be frequently too high. This is possibly due in part to the excess repulsions between atoms separated by distances just greater than normal covalent bond distances. This inaccuracy was greatly reduced in progression from the MNDO method (released in 1977) to the AM1 method (1985), and has been further improved in the PM3 method (1989).⁵¹

From the calculations of the compounds in this thesis several points can be made. For the two cyclohexa-2,4-dienones with methyl substituents at both C2 and C6, namely the 3,4,6-trichloro-2,6-dimethyl dienone (48) and 4,5,6-trichloro-2,6-dimethyl dienone (49), and the 4,6-dichloro-2,3,6-trimethyl dienone (131) and 4,6-dichloro-2,5,6-trimethyl dienone (132) studied by B. A. Wells⁵⁴, the AM1 calculations appear to estimate the energies of the minor conformer as being too stable. However, very small errors in the energies will have a large effect on the Boltzmann distribution. For these two dienone pairs the PM3 method appears to be more accurate. These were the only two dienones in which both isomers were found experimentally.



For cyclohexadienones with a chloro substituent at C2 the barriers to interconversion for these compounds were very similar to those of the two 2,6-dimethyl dienone pairs, however, no 6-chloro-6-methylcyclohexa-2,4-dienone isomer was seen to arise from the 2-chloro-6-methyl dienones (63), (17), (33), (100) and (85). The PM3 method consistently failed to predict the ratio of conformers accurately. The best case predicted ratio was 44 : 56 [(100) and (106) (over)] compared with the experimental value of 100 : 0. The AM1 calculated ratios, however, appeared to be closer to the experimental results. The worst case results predicted 64 : 36 [(85), (96) and (100), (106) (over)] compared with the experimental value of 100 : 0. The best case AM1 result was still predicting 8% of the minor dienone (118) when this compound was not seen experimentally.

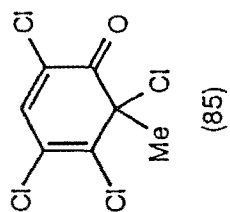
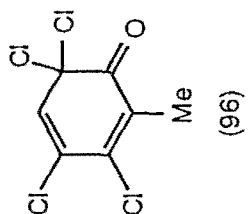
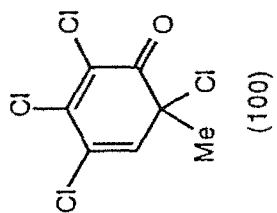
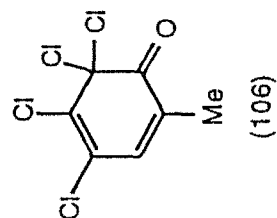


Table 6.11
Semi-Empirical Calculation Results (kJ mol⁻¹)

cyclohexa-2,4-dienone				Boltzmann Ratio (1) : (2)	$\Delta(\Delta H_f)$ [(1)→TS]
	ΔH_f (1)	ΔH_f (TS)	ΔH_f (2)		
3,4,6-trichloro-2,6-dimethyl-	(48)		(49)	expt. 41 : 59	
(AM1)	-128.09	36.90	-127.69	54 : 46	164.99
(PM3)	-155.65	-18.18	-155.78	49 : 51	137.47
4,6-dichloro-2,3,6-trimethyl-				expt. 84 : 14 ⁵⁴	
(AM1)	-135.6	28.5	-135.2	54 : 46	164.1
(PM3)	-170.4	-31.6	-166.0	85 : 15	138.8
2,4-dichloro-6-methyl-	(63)		(82)	expt. 100 : 0	
(AM1)	-98.04	68.24	-96.85	88 : 12	166.28
(PM3)	-121.81	17.25	-123.35	7 : 93	139.06

Table 6.11 (cont.)
Semi-Empirical Calculation Results (kJ mol⁻¹)

cyclohexa-2,4-dienone	ΔH_f (1)	ΔH_f (TS)	ΔH_f (2)	Boltzmann Ratio (1) : (2)	$\Delta(\Delta H_f)$ [(1)→TS]
2,4-dichloro-3,6-dimethyl-	(17)		(122)	expt. 100 : 0	
(AM1)	-121.83	45.78	-119.14	75 : 25	167.61
(PM3)	-156.99	-16.75	-158.34	37 : 63	140.24
2,4-dichloro-5,6-dimethyl-	(33)		(118)	expt. 100 : 0	
(AM1)	-122.15	44.94	-116.30	92 : 8	167.09
(PM3)	-155.60	-3.41	-157.69	30 : 70	159.01
2,3,4-trichloro-6-methyl-	(100)		(106)	expt. 100 : 0	
(AM1)	-112.63	55.41	-111.25	64 : 36	168.04
(PM3)	-139.76	0.61	-140.40	44 : 56	140.37
2,4,5-trichloro-6-methyl-	(85)		(96)	expt. 100 : 0	
(AM1)	-112.63	54.24	-111.24	64 : 36	166.87
(PM3)	-140.51	0.63	-141.65	39 : 61	141.14

6.9 APPENDIX 3: REACTION HALF LIFE STUDIES

In a effort to determine the effect of hydrogen chloride on the rate of reaction of a cyclohexadienone reacting with chlorine by nucleophilic mechanisms a study was undertaken to measure the approximate half life of the reaction. A sample of one of three cyclohexadienones (*c.* 2.350×10^{-4} mol) was dissolved in acetic acid and a solution of chlorine (1.2 mol equivalents) in acetic acid was added, such that the total volume of acetic acid was 750 μ l. The mixture was stirred for 30 min. before the solvent was removed and a ^1H n.m.r. spectrum was taken. From the amount of unreacted dienone remaining the half life was estimated. This reaction was repeated using acetic acid containing 1% conc. hydrochloric acid, and the resulting mixture analysed in the same manner. To demonstrate that the catalysis was by hydrogen chloride, and not by water or by any acid, the reaction was also carried out in acetic acid containing 1% phosphoric acid and in acetic acid containing 1% distilled water.

It was believed prior to this study that nucleophilic addition of chlorine to a cyclohexadienone by a nucleophilic mechanism was specifically hydrogen chloride catalysed. As shown in Table 6.12 (over) the half lives of the reactions of all three cyclohexadienones showed a dramatic decrease on addition of hydrochloric acid to the solvent, indicating that HCl is an effective catalytic agent in these reactions. Phosphoric acid showed some catalytic properties for two of the cyclohexadienones [(63) and (85)]; this was not unexpected as the reaction is believed to involve charged intermediate species, and increasing the ionic strength of the solvent will stabilise these intermediates, leading to an increase in the rate of reaction. It is not known why the reaction of the 2,4,6-trichloro-5,6-dimethyl dienone (33) was slower with added phosphoric acid. The reactions with added water gave very surprising results. For all three cyclohexadienones this reaction proved to be faster than the reaction with

added hydrochloric acid. It is not known why this occurs but this result can not be accommodated under the existing mechanism for nucleophilic addition of chlorine.

Table 6.12

Estimated Half Life of Reaction with Chlorine (minutes)

in AcOH with added:	-cyclohexa-2,4-dienone		
	2,4,6-trichloro-6- methyl- (63)	2,4,6-trichloro-5,6- dimethyl- (33)	2,4,5,6-tetrachloro- 6-methyl- (85)
-	30.0	15.6	192
HCl	5.9	10.7	17.4
H ₃ PO ₄	24.2	40.0	25.9
H ₂ O	11.7	8.8	15.3

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